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(54) **CHIRAL STATIONARY PHASES FOR ENANTIOMERS SEPARATION AND THEIR PREPARATION**

CHIRALE STATIONÄRE PHASEN FÜR DIE TRENNUNG VON ENANTIOMEREN UND IHRE HERSTELLUNG

PHASES STATIONNAIRES CHIRALES POUR ENANTIOMERES ET LEUR PREPARATION

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Description

State of the art

[0001] The separation of enantiomers by means of liquid chromatography (LC) using chiral stationary phases is based on the reversible diasteromeric association between the chiral environment in the column and the enantiomers in the solution (S. Allenmark, "Chromatographic Enantioseparation", 2nd Edition, Ellis Horwood, New York, 1991, pp. 1007-1008).

[0002] The chiral stationary phases for LC are normally classified on the basis of their general structures. One group is based on either synthetic or natural polymers and is totally or intrinsically chiral.

[0003] Another group is made up of chiral selectors with a low molecular weight bound to a solid, incompressible, matrix, generally silica. The latter provides remarkable advantages with respect to the former since the chiral selectors can be designed rationally (K.B. Lipkowitz, Modelling Enantiodifferentiation in Chiral Chromatography, in "A Practical Approach to Chiral Separation by Liquid Chromatography", G. Subramanian Editor, VCH, Weinheim, 1994, pp. 19-55).

[0004] This implies that they can be selected on a rational basis; in fact, their enantioselective features can often be evaluated by means of NMR studies or can be singled out thanks to computer modelling according to the various types of chemical interactions.

[0005] Among the most frequently used chiral selectors bound to a solid support it is worth quoting the "crown ethers" (E.P. Kyba et al., *J. Am. Chem.* Soc., 1978, 100: 4555-4568), the charge-transfer complexes (W.H. Pirkle et al., *J. Am. Chem. Soc.* 1986, 108: 352) the chiral selectors based on hydrogen bonds (see e.g. S. Hara et al., *J. Chromatogr.*, 1979, 186: 543) and other types of chiral selectors (P. Salvadori et al., *Tetrahedron*, 1987, 43, 4969).

[0006] All these products exhibit some limitations with respect to their enantioseparating ability, which are due either to the high number of functional groups or structural subunits that participate in the interaction with the enantiomers in solution.

[0007] The range of application of chiral selectors should therefore be widened up so as to promote the use and versatility of chromatography based on stationary chiral phases. 1,3-dicyano-2,4,5,6,-tetrachlorobenzene is a fungicide widely used in agriculture; some of its derivatives such as glutathione are described in *Tetrahedron,* 1995, 51: 2331. None of these derivatives is used in chromatography.

Field of the invention

[0008] This invention relates to new derivatives of 1,3-dicyanobenzene containing one or more chiral groups and one group acting as a spacer. The stationary phases obtained from these derivatives provide an efficient separation of enantiomers.

Summary

[0009] The present invention describes new chiral stationary phases, and the optically active compounds therein contained. The optically active compounds contained in the stationary phases are represented by the formula of structure (I), which comprise at least one asymmetric carbon atom and a substituent acting as a spacer. The stationary phases of the present invention can be used in the preparation of chromatographic columns useful for the analytical and preparative separation of enantiomers.

Brief description of the figures

[0010]

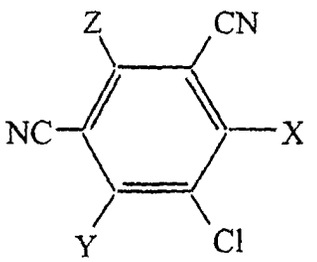
Figure 1: preparation of the FSC 1 chiral stationary phase
Figure 2: preparation of the FSC 5 chiral stationary phase
Figure 3: preparation of the FSC 10 chiral stationary phase
Figure 4: preparation of the FSC 20 chiral stationary phase
Figure 5a-p: Z, X and Y substituents of the chiral stationary phases (1)-(28) as prepared in the experimental part. The reference structure is that of formula (I).
Figure 6: list of racemic mixtures

Detailed description of the invention

[0011] The present invention regards chiral stationary phases for chromatography based on new chiral derivatives,

hereinafter referred to as "chiral selectors".

[0012] The chiral selectors, that form the first object of the present invention are represented by the general formula (I):



I

where:

$X=NR_1\text{-}CHR_2R_3$

R_1 represents H, alkyl C_1-C_6 linear or branched,

R_2 represents H, alkyl C_1-C_6 linear or branched, aryl or arylalkyl possibly containing an heteroatom, being said aryl or arylalkyl optionally substituted with - OH, $-CH_2CONH_2$,

R_3 represents:

alkyl C_1-C_6 linear or branched, $(CH_2)_p$-COOH, $(CH_2)_p$-$CONH_2$, $(CH_2)_p$-$CONHR_4$, $(CH_2)_p$-$NHCOR_4$, $(CH_2)_p$-$CON(R_4R_5)$, $CONHCH(R_4)$ $CONHR_4$, $(CH_2)_p$-$NHCOCH(R_4)NHCOR_4$, C_6H_4-CH_2-$NHCOCH(R_4)$ $NHCOR_4$, $CH_2NH(CH_2)_p$-$NHCOCH(R_4)NHCOR_4$

where p is an integer from 0 to 4, **R_4** and **R_5** independently of each other represent (a) alkyl C_1-C_6 linear or cyclic, (b) aryl, (c) a spacer group of formula $(CH_2)n\text{-}Si\text{-}(OR_6)_3$ where n is comprised between 1 and 10 and R_6 represents an alkyl C_1-C_4; said groups (a) and (b) are optionally substituted with alkyl C_1-C_4, aryl, cycloalkyl C_5-C_6, NO_2, OCH_3,, or:

(i) R_1 forms together with R_2, with the carbon atom bound to R_2 and with the nitrogen, a 5-6 membered ring, or

(ii) R_2 forms with R_3 and with the carbon atom bound to R_2 and R_3 a 5-6 membered ring substituted by $-NHCOR_4$, or by $-NHCOCH(R_4)NHCOR_4$, R_4 being as above defined;

Y e **Z** independently of each other represent: chloro, X group where X has the meanings given above, a spacer group of formula $-A(CH_2)n\text{-}Si\text{-}(OR_6)_3$ where A represents NH or O, preferably NH, and n and R_6 have the meanings given above; with the proviso that said formula (I) contains: (a) one to three X groups containing at least one chiral atom, and (b) only one spacer group as above defined.

[0013] Generally, in formula (I), the X group represents preferably an α-aminoacid, ester of aminoacid, amide of aminoacid, arylalkylalcohol, arylcarboxylic acid, arylcarboxylic acid ester, arylcarboxylic acid ester, aminoamide, arylalkylamine.

[0014] The arylalkyl groups quoted above are preferably represented by the benzyl group.

[0015] The aryl groups are preferably represented by either phenyl or naphthyl.

[0016] The derivatives of formula (I) always contain at least one chiral carbon atom. This carbon atom is always contained in the X group and is normally represented by the carbon C* of the $C^*HR_2R_3$ group or it is contained in the R_3 substituent.

[0017] Within the formula (I) herein defined, it is possible to identify subgroups of products particularly useful for the purpose of this invention.

[0018] A first group of selectors preferred is represented by formula (I) where:

R_1 represents H, alkyl C_1-C_6 linear or branched, R_2 represents H, alkyl C_1-C_6 linear or branched, aryl, arylalkyl, CH_2CONH_2, or R_1 forms with R_2, with the carbon atom bound to R_2 and with N a 5-6 membered ring; R_3 represents alkyl C_1-C_6 linear or branched, $(CH_2)_p$-$CONHR_4$, $(CH_2)_p$-$CON(R_4R_5)$, where p, R_4 and R_5 have the meanings given above.

[0019] A second group of selectors preferred is represented by formula (I) where:

R_1 represents H, R_2 represents: H, R_3 represents $(CH_2)_p$-$NHCOR_4$, CH_2-$NHCOR_4$,

where p, R_4 have the meanings given above; or R_2 forms with R_3 and the carbon atom bound to R_2 and R_3 a 5-6 membered ring.

[0020] A third group of preferred selectors is represented by formula (I) where:

R_1 represents H, , R_2 represents H, or R_2 forms with R_1 , with the carbon atom bound to R_2 and with N a 5-6 membered ring; R_3 represents $CONHCH(R_4)CONHR_4$, where p, R_4 have the meanings given above.

[0021] A fourth group of selectors preferred is represented by formula (I) where:

R_1 represents H, R_2 represents H, , R_3 represents:, $(CH_2)_p$-$NHCOCH(R_4)NHCOR_4$, C_6H_4-CH_2-$NHCOCH(R_4)NHCOR_4$, $CH_2NH(CH_2)_p$-$NHCOCH(R_4)NHCOR_4$,; or R2 forms with R3 and with the carbon atom bound to R2 and R3 a 5-6 membered ring substituted with $NHCOCH(R_4)NHCOR_4$; p and R_4 having the meanings given above.

[0022] Preferred selectors of formula (I) are quoted in the following list. The names in bracket refer to the corresponding chiral stationary phases whose structure are reported in figure 5:

5-Chloro-4,6-di-[R-1-(naphth-1-yl)ethyl]amino-2-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene (FSC 1)

4-[(3,5-dimethylanilido)-L-phenylalaninyl]-6-(3-triethoxysilyl)propylamino-2,5-dicloro-1,3-dicyanobenzene, and 4-[(3,5-Dimethylanilido)-L-phenylalaninyl]-2-(3-triethoxysilyl)propylamino-5,6-dicloro, 1,3-dicyanobenzene (FSC 3)

4-[(naphth-1-yl)amido)-L-phenylalaninyl]-2-(3-triethoxypropyl)amina-5,6-dichloro-1,3-dicyanobenzene and 4-[(Naphth-1-yl)amido)-L-phenylalaninyl]-6-(3-triethoxypropyl)amino-2,5-dichloro-1,3-dicyanobenzene (FSC 4)

4-[R-1-(naphth-1-yl)ethyl]amino-2-(3-triethoxysilylpropyl)amino-5,6-dichloro-1,3-dicyanobenzene and 4-[R-1-(naphth-1-yl)ethyl]amino-6-(3-triethoxysilylpropyl)amino-2,5-dichloro-1,3-dicyanobenzene (FSC 6)

4-{n-butyl-[R-1-(naphth-1-yl)ethyl]acetamido}amino-6-(3-triethoxysilylpropyl)amino-2,5-dichloro-1,3-dicyanobenzene, and 4-{n-butyl-[R-1-(naphth-1-yl)ethyl]acetamido}amino-2-(3-triethoxysilylpropyl)amino-5,6-dichloro-1,3-dicyanobenzene (FSC 7)

4-{n-butyl-[R-1-(cyclohexyl)ethyl-N-R-(naphth-1-yl)methyl]acetamido}amino-6-(3-triethoxysilylpropyl)amino-2,5-trichloro-1,3-dicyanobenzene and 4-{n-butyl-[R-1-(cyclohexyl)ethyl-N-R-(naphth-1-yl)methyl]acetamido}amino-2-(3-triethoxysilylpropyl)amino-5,6-trichloro-1,3-dicyanobenzene (FSC 8)

4-{n-butyl-[N-R-1-(cyclohexyl)ethyl-N-3,5-dinitrobenzyl]acetamido}amino-6-(3-triethoxysilylpropyl)amino-2,5-dichloro-1,3-dicyanobenzene and 4-{n-butyl-[N-R-1-(cyclohexyl)ethyl-N-3,5-dinitrobenzyl]acetamido}amino-2-(3-triethoxysilylpropyl)amino-5,6-dichloro-1,3-dicyanobenzene (FSC 9)

4-{2-[2-(6-methoxy-naphth-2-yl)-propionylamido]ethyl}amino-6-(3-triethoxysilylpropyl)amino-2,5-dichloro-1,3-dicyanobenzene and 4-{2-[2-(6-methoxy-naphth-2-yl)-propionylamido]ethyl}amino-2-(3-triethoxysilylpropyl)amino-5,6-dichloro-1,3-dicyanobenzene (FSC 10)

4-{methyl-[R-1-(naphth-1-yl)ethyl]acetamido}amino-2-(3-triethoxysilylpropyl)amino-5,6-dichloro-1,3-dicyanobenzene, and 4-{methyl-[R-1-(naphth-1-yl)ethyl]acetamido}amino-6-(3-triethoxysilylpropyl)amino-2,5-dichloro-1,3-dicyanobenzene (FSC 11)

4-[3,5-dimethylanilido)-L-alaninyl]-2,5-dichloro-6-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene, and 4-[3,5-dimethylanilido)-L-alaninyl]-5,6-dichloro-2-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene (FSC 14)

4-(cyclohexylamido-L-alaninyl)-2,5-dichloro-6-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene, and 4-(cyclohexylamido-L-alaninyl)-5,6-dichloro-2-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene (FSC 15)

4-[(3,5-dimethylanilido)-prolinyl]-2,5-dichloro-6-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene, and 4-[(3,5-dimethylanilido)-prolinyl]-5,6-Dichloro-2-(3-triethoxysilylpropyl)amino 1,3-dicyanobenzene (FSC 16)

4-(prolinyl-cyclohexylamide)-2,5-dichloro-6-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene, and 4-(prolinyl- cyclohexylamide)-5,6-dichloro-2-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene (FSC 17)

4-[L-prolinyl-L-alanilyl-(3,5-dimethylanilide)]-2,5-dichloro-6-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene, and 4-[L-prolinyl-L-alanilyl-(3,5-dimethylanilide)]-2,5-dichloro-2-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene (FSC 18)

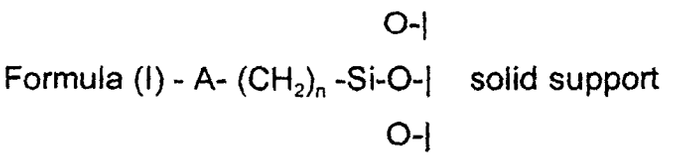
4-{[2-(3,5-dinitrobenzoyl)-cyclohexyl]amide}-2,5-dichloro-6-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene, and 4-{[2-(3,5-dinitrobenzoyl)-cyclohexyl]amide)amino-5,6-dichloro-2-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene (FSC 22)

4-{2-[2-(6-methoxy-naphth-2-yl)-propionylamido]cyclohexyl}amino-6-(3-triethoxysilylpropyl)amino-2,5-dichloro-

1,3-dicyanobenzene and 4-{2-[2-(6-methoxy-naphth-2-yl)-propionylamido]cyclohexyl}amino-2-(3-triethoxysilylpropyl)amino-5,6-dichloro-1,3-dicyanobenzene (FSC 23)

[0023] Formula (I) entails the presence of at least one X chiral substituent bound in meta position with respect to the Z group. When Y=X, formula (I) can contain two chiral groups in meta position with respect to the Z group, by conferring thus specific symmetry characters: if the two X substituents are structurally and stereochemically different from one another, the molecule acquires C1 symmetry; on the other side if the two X substituents are structurally and stereochemically identical, the molecule acquires C2 symmetry. Another possibility of having a chiral selector of formula (I) with two chiral groups on the tetrachlorodicyanobenzene is allowed when Z=X.

[0024] Formula (I) always contains one spacer group as above defined. Preferred spacer groups are those where R_6 represents ethyl and n is 3. A most preferred spacer is the (3-triethoxylsilylpropyl)amino group. As evident from formula (I), the spacer group can be indifferently present as an Y, Z group or as a further substituent of the chiral group. In this latter case (i.e. when the spacer is defined by the substituent R_4 or R_5, option (c)), the R_3 substituents are preferably chosen among: $(CH_2)_p$-$CONHR_4$, $(CH_2)_p$-$CON(R_4R_5)$, $CONHCH(R_4)$ $CONHR_4$.By means of a covalent binding that involves the oxygen atoms of the $(OR_6)_3$ groups, the spacer group allows to bind the molecule of formula (I) to a solid support and to form chiral stationary phases for chromatography. The linkage that forms can be represented in this way:



[0025] The solid support can be of either of organic or, preferably, inorganic type. Suitable examples of solid inorganic support are silica gel, alumina, kaolin, titanium oxide, magnesium, silicate, synthetic polymers. The preferred solid support is silica (e.g. silica gel).

[0026] The present invention relates also to a process for the production of chiral stationary phases. This process entails the use of 1,3-dicyano-2,4,5,6-tetrachlorobenzene as a reagent; as mentioned above, this product is commercially available.

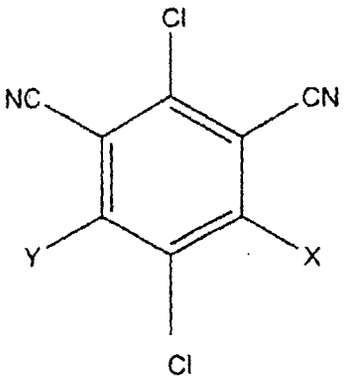
[0027] In agreement with the structural requirements of formula (I), the present process entails the introduction of only one spacer group, and from one to three chiral X groups.

[0028] The process is thus characterised by comprising the following separate reaction steps which can take place in any order:

- introduction of one or more chiral X groups on the dicyanobenzene ring,
- introduction of the spacer group either on dicyanobenzene ring or on a chiral group already present on the dicyanobenzene ring,
- formation of covalent linkage between the spacer group and a solid support.

[0029] According to a first specific embodiment, the above described process comprises the following steps:

a) introduction of one or more chiral X groups on the 1,3-dicyano-2,4,5,6-tetrachlorobenzene by substitution of one or both chlorine atoms in position 4 or 6 with the obtainment of chiral derivatives of formula (II).



Formula (II)

where X and Y have the meanings defined above, with the only difference that they do not contain any spacer group.
b) introduction of a spacer group in the derivative of formula (II) obtained in step a), wherein said spacer group is introduced either by substitution of one chlorine atom on the dicyanobenzene ring or it is introduced on the X group, with the obtainment of the chiral selector of formula (I).
c) formation of covalent linkage between the spacer group and the solid support with the obtainment of the chiral stationary phase.

[0030] According to a second specific embodiment, the above described process comprises the following steps:

a) introduction of one or more chiral X groups on the 1,3-dicyano-2,4,5,6-tetrachlorobenzene by substitution of one or both chlorine atoms in position 4 or 6 of the dicyanobenzene ring with the obtainment of chiral derivatives of formula (II).
b) formation of covalent linkage between a spacer group and a solid support.
c) introduction of the spacer group linked to the solid support obtained in step b) either on position 2 or 4 or 6 of the dicyanobenzene ring or on the X group of chiral selector of formula (II) obtained in a) with the obtainment of the chiral stationary phase.

[0031] According to a third specific embodiment, the above described process comprises the following steps:

a) introduction of a spacer group on 1,3-dicyano-2,4,5,6-tetrachlorobenzene by substitution of one chlorine atom in position 4 or 6 of the dicyanobenzene ring, where said spacer group is possibly previously bounded to the solid support b) introduction of one or more chiral X groups on the dicyanobenzene ring by substitution of either one or both chlorine atoms in position 2 or 4 or 6 of the compound of step a), possibly formation of covalent linkage between the spacer group and the solid support, with the obtainment of chiral stationary phases.

[0032] The chiral X groups are introduced in the 1,3-dicyano-2,4,5,6-tetrachlorobenzene by substitution of one or more of the chlorine atoms in position 2,4,6, using suitable reagents containing the X group.

[0033] Examples of these reagents are α-aminoacids, α-arylalkyl amine, secondary alcohols, amides or esters of chiral carboxylic acids. Examples of specific reagents are: 1-phenylethylamine, proline, (1-(naphth-1-yl)ethylamine, phenylalanine, phenylglycine, n-butylamine, naphthylethylamine, 3,5-dimethylaniline, cyclohexylethylamine, sarcosine, asparagine.

[0034] The spacer group is preferably introduced by reaction with a reagent of formula AH-(CH_2)n-Si-$(OR_6)_3$ where A=NH_2, OH, and where n and R_6 have the meanings described above.

[0035] The introduction of X, Y and Z groups is performed by heating the reagents in a suitable solvent, possibly in the presence of an excess of this solvent. The operational temperature ranges from 20°C to 150°C and the reaction time ranges from 60 minutes to 80 hours. When a single X group is introduced in the ring, then the reaction is preferably performed in a polar solvent or in a mixture of solvents. Moreover the times are shorter, ranging from 1 to 5 hours. In case derivatives with two X substituents are to be prepared then it is preferable to use an excess of liquid reagent (molar excess 50 - 100 times) and then carry on heating up to 80 hours.

[0036] The X chiral groups that are present in the stationary phases that are the object of this invention are in an optically pure form, that is they have a specific stereochemical configuration. The synthesis of the products of formula (II) and (I) that are the object of the present invention are carried out by using the nucleophylic reagents containing the X group in an optically pure form.

[0037] The covalent binding between the spacer group and the solid support is obtained according to known chemical

reactions comprising heating at high temperature in the presence of an organic solvent.

[0038] The preparation of the chiral stationary phases based on chiral selectors of formula (I), and the specific structures of some chiral stationary phases are shown in Figures 1-5.

[0039] Figure 1,2,3,4 show the preparation of stationary chiral phases called *FSC 1, 5, 10, 20.* The experimental part reports the preparation of stationary phases starting from a variety of chiral selectors of formula (I).

[0040] The stationary phases (whose structures are illustrated in Figure 5) that are the object of the present invention allow the separation of several racemic mixtures of commercial interest. The use of these chiral stationary phases for the enantiomeric separation by chromatography, and in particular their use in the preparation of high performance liquid chromatographic columns (HPLC) constitutes a further aspect of the present invention. Moreover, the present invention comprises a method of separation of enantiomeric mixtures by means of such chiral stationary phases. Examples of isomer separation by means of stationary phases object of the invention are reported in the experimental part.

[0041] The stationary phases which are object of the present invention allow both the analytical and preparative separation of enantiomers of structurally different compounds and to determine the enantiomeric composition obtained by means of various asymmetric syntheses (V. Vinkovic et al., Tetrahedron, 1997, 53, 689; E. Ljubovic, et al. *Tetrahedron: Asymm*., *1997,* 8, 1).

[0042] The separation process takes place by means of several efficient interactions for the enatioselection and also by means of new kinds of cumulative interaction that can be performed specifically and only by means of the selectors of formula (I) claimed in the present invention. In particular, the high electronegativity of the chlorine atom and the dipolar moment of the CN group of the chiral selector promotes the setting of polar interactions and the formation of hydrogen bonds with the enantiomers to be separated.

[0043] Moreover, the lack of π electrons on the aromatic ring that is measured with the sum of the σ constants of each substituents (chlorine, cyano- amino, amido, alkoxy) is higher than the one calculated for the amide derivative of N-(3,5-dinitrobenzoyl)-aminoacid used by Pirkle as a chiral selector (Pirkle, *J. Am. Chem. Soc.* 1986, 108, 352). The new stationary phases are therefore remarkably more effective in the formation of interactions of the π-π kind with strong π-donor groups present in the chiral compounds to be separated. In particular, the stationary phases claimed turned out to be effective in the separation of a wide number of enantiomers such as α-aminoacids and of their derivatives with N- and O-protection, carboxylic acids and their esters or heterocyclic or acyclic amides, amines, alcohols, thiols, epoxides and aziridines.

[0044] The examples listed hereunder aim at illustrating the invention without a limitative purpose.

EXAMPLES

Examples of preparation of chiral selectors and stationary phases

Example 1 *5-Chloro-4,6-di-[R-1-(naphth-1-yl)ethyl]amino-2-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene*

[0045] The mixture of 2,4,5,6-tetrachloro-1,3-dicyanobenzene (2.0 g; 7.5 mmol) and [R-1-(naphth-1-yl)ethyl]amine (5.13 g; 30.0 mmol) is heated at 100°C in DMF (30 ml) for 48 hr. Then the solvent is evaporated to dryness, the crude product dissolved in toluene and purified by chromatography on silica gel column (100 g), using toluene as eluent. It is obtained 3.78 g (93%) of slightly yellow crystals of the pure product: 2,5-dichloro-4,6-di-[R-1-(naphth-1-yl)ethyl] amino-1,3-dicyanobenzene. The analysis of this product is as follows: Anal. calcd. for $C_{32}H_{24}N_4Cl_2$:C 71.77, H 4.51 and N 10.4. Found: C 71.72, H 4.56 and N 10.42%.

[0046] This compound (3.28 g, 6.13 mmol) in excess of 3-aminopropyltriethoxysilane (10.0 ml, 42.5 mmol) is heated at 110°C for 24 hrs. The solution is cooled to room temperature, diluted with toluene, applied on to flash chromatography column with silica gel and eluted with toluene. The pure product (3.85 g, 87 %) is isolated as pale-yellow oil.
IR (KBr): 3400, 3060, 2980, 2920, 2200, 1590, 1510, 1470, 1450, 1390, 1380, 1360, 1300, 1260, 1230, 1200, 1160, 1100, 1080, 1010, 950, 860, 800, 780, 720 cm^{-1}.
Anal. calcd. for $C_{41}H_{46}N_5SiO_3Cl$ (720.36); C 68.35, H 6.43, N 9.72, Found; C 68.31, H 6.48, N 9.68 %.

Example 2: *Chiral stationary phase* ***FSC*** *1*

[0047] The compound of example 1 (7.70 g; 10.6 mmol) and silica gel LiChrospher Si 100 (4.18 g) are heated under reflux in dry toluene over 72 hr. Chiral stationary phase *FSC 1* (5.7 g) is isolated as pale-yellow amorphous material.

[0048] Analysis, found; C 17.81, H 2.00, N 2.77 %. According to elemental analysis it is calculated that 0.21 mmol of the chiral selector is bound on 1.0 g of silica gel.

Example 3: *4-N-L-Phenylglycinyl-2,5,6-trichloro-1,3-dicyanobenzene*

[0049] To 2,4,5,6-tetrachloro-1,3-dicyanobenzene (4.0 g, 15.0 mmol) in MeOH (100 ml) is added to a warm solution of L-phenylglycine (4.55 g, 30.0 mmol) and sodium carbonate (3.18 g, 30.0 mmol) in water (100 ml). The reaction mixture is stirred and heated under reflux for 1.5 hr, then cooled and filtered. The filtrate is acidified by addition of 1M HCl (50 ml), and the precipitated product is separated by filtration. It is washed with water and dried *in vacuo* at ambient temperature. Crystallisation from ethanol afforded 1.40 g (25%) of pure product, white powder.

[0050] IR (KBr): 3500, 3320, 2220, 1715, 1570, 1500, 1450, 1380, 1310, 1290, 1260, 1210, 1180, 1120, 1070, 1040, 1000, 960, 910, 860, 760, 720, 690 cm^{-1}.

[0051] Anal. calcd. for $C_{16}H_8N_3O_2Cl_3$ (380.60 g/mol): C 50.48, H 2.11 and N 11.04. Found: C 50.53, H 2.36 and N 10.86%.

Example 4: *Chiral stationary phase **FSC** 5*

[0052] A mixture of silica gel LiChrospher 100 NH2 (2.00 g, 1.4 mmol of N_2), chiral prepared in the Example 3, (0.628 g, 1.59 mmol) and EEDQ (0.39 g, 1.59 mmol) is stirred in dichloromethane (10 ml) at room temperature for 16 hr. After addition of methanol (50 ml) stirring is continued for 30 min. The stationary phase is then separated by filtration, is washed with methanol, then dried at 70°C for 4 hr. 2.15 g of the stationary phase FSC 5 are obtained.

[0053] Anal. found: C 8.08%, H 1.05%, N 1.66%. The % of N reveals that 1.0 g of the stationary phase contains 0.39 mmol of chiral selector.

Example 5: *4-{n-butyl-[R-1-(cyclohexyl)ethyl-N-R-(naphth-1-yl)methyl]acetamido}amino-2,5,6-trichloro-1,3-dicyanobenzene*

[0054] R-1-(Cyclohexyl)ethylamine (CEA) (1.59 g, 12.5 mmol) and 1-chloromethylnaphthalene (2.45 g, 12.5 mmol) are dissolved in methanol (5 ml). Triethylamine (5 ml) is added. Reaction solution is heated for 3 hr under reflux, then evaporated to dryness. The solid residue is dissolved in dichloromethane (50 ml). The organic solution is washed with 1M aq. sodium bicarbonate, then with water. It is filtered through cotton-plug and evaporated. It afforded the oily N-(naphth-1-yl)-R-1-(cyclohexyl)ethylamine (2.23 g. 65%). The amine (2.13 g, 8 mmol) is then dissolved in dichloromethane (25 ml) and triethylamine (0.81 g, 8.0 mmol) added. To this solution isochloroacetyl chloride (0.90 g, 9.0 mmol) in dichloromethane (25 ml) is added dropwise. After 1 hr stirring at ambient temperature reaction solution is washed with 1M aq. bicarbonate. The organic phase is filtered through a cotton-plug and evaporated leaving 2.70 g (98%) of N-chloroacetyl-N-(naphth-1-yl)methyl-R-cyclohexylamine. This product is dissolved in methanol (10 ml), then n-butanol (5 ml) is added, and the reaction solution is heated under reflux for 5 hr. On evaporation to dryness, the residual oil is dissolved in dichloromethane (50 ml), then it is washed with 1M bicarbonate and water, filtered and evaporated, affording an oily product (3.01 g, 99%). Said amine (2.79 g, 7.33 mmol) and 2,4,5,6-tetrachloro-1,3-dicyanobenzene (0.97 g, 3.65 mmol) are heated in acetonitrile (20 ml) under reflux for 2 hr. On evaporation to dryness, the residue is dissolved in toluene and purified by chromatography on silica gel (40 g), using first toluene then toluene/acetone (30:1) as eluent. On evaporation of the fractions containing the pure product, 1.70 g (76%) of the pure title compound are obtained.

IR (KBr): 3030, 2920, 2850, 2220, 1650, 1600, 1550, 1510, 1450, 1410, 1375, 1310, 1220, 1200, 1175, 1125, 1065, 980, 910, 800, 770, 730, 695, 650, 620 cm^{-1}.

Anal. calcd. for $C_{33}H_{35}N_4OCl_3$ (609.99 g/mol): C 64.97, H 5.78, and N 9.18. Found: C 65.01, H 5.89, and N 9.15%.

Example 6: *4-{n-butyl-[R-1-(cyclohexyl)ethyl-N-R-(naphth-1-yl)methyl]acetamido}amino-6-(3-triethoxysiyspropyl) amino-2,5-trichioro-1,3-dicyanobenzene and 4-{n-butyl-[R-1-(cyclohexyl)ethyl-N-R-(naphth-1-yl)methyl]acetamido} amino-2-(3-triethoxysilylpropyl)amino-5,6-trichloro-1,3-dicyanobenzene*

[0055] The chiral selector (1.00 g, 1.63 mmol) prepared in the Example 5 and 3-aminopropyltriethoxysilane (APTES) (3.0 ml) are heated at 100°C for 1 hr. The crude product is purified by chromatography on silica gel column (30 g) using first toluene then toluene/acetone (30:1) as eluent. On evaporation of fractions containing the product, 0.99 g (76%) of pure product are obtained, as a mixture of title isomers (3:1).

IR (KBr): 3400, 3340, 2960, 2920, 2720, 2200, 1650, 1570, 1510, 1460, 1440, 1410, 1390, 1360, 1340, 1300, 1260, 1220, 1200, 1160, 1100, 950, 890, 840, 790, 770, 680 cm^{-1}.

Anal. calcd. for $C_{42}H_{57}N_5SiO_4Cl_2$ (794.89 g/mol): C 63.45, H 7.22, and N 8.81. Found: C 63.49, H 7.48, and N 8.88%.

Example 7: *Chiral stationary phase **FSC** 8*

[0056] A mixture of isomers (0.90 g, 1.15 mmol) as prepared in the Example 6 and

[0057] Nucleosil 100-5 (2.03 g) are heated under reflux in dry toluene (5 ml) for 20 hr. The silica gel is filtered off, is washed with cold toluene, and dried *in vacuo* at 70°C for 4 hr. It is obtained 2.26 g of the chiral stationary phase ***FSC** 8.*

[0058] Anal found: C 8.73%, H 1.62% and N 1.46%. According on % of N it is calculated that 0.21 mmol of chiral selector is bound at 1 g of chiral stationary phase.

Example 8: *4- {2-[2-(6-methoxy-naphth-2-yl)-propionylamido]ethyl}amino-2,5,6-trichloro-1,3-dicyanobenzene*

[0059] 2,4,5,6-Tetrachloro-1,3-dicyanobenzene (5.0 g, 18.8 mmol) and 1,2-diaminoethane (5.0 ml) are stirred in methanol (100 ml) for 1 h at ambient temperature. The precipitate is collected on filter and is washed with methanol, then acetone, affording 4.41 g (81%) of pure product as pale-yellow powder:4-(2-aminoethylamino)-2,5,6-trichloro-1,3-dicyanobenzene. This product is characterised as follows: Anal calcd. for $C_{10}H_7N_4Cl_3$ (289.54 g/mol): C 41.47, H 2.43, and N 19.35. Found: C 41.62, H 2.46, and N 19.23%.

[0060] 2-(6-Methoxy-naphth-2-yl)-propionic acid (0.50 g, 2.17 mmol) is dissolved in THF (5.0 ml). To the solution DCC (0.45 g, 2.17 mmol) in THF (5.0 ml) is added and then the compound above prepared (0.63 g, 2.2 mmo) in dry THF (10 ml) is added. After 2 h stirring at ambient temperature reaction mixture is filtered through a cotton plug. The filtrate diluted with 2-propanol (50 ml) and evaporated to final volume of ca 10 ml. On cooling pure product is precipitated, on after washing with 2-propanol and drying 0.85 g (78%) of pure product are obtained.

[0061] IR (KBr): 3380, 3220, 3180, 3040, 2950, 2220, 1650, 1610, 1570, 1510, 1450, 1390, 1340, 1300, 1260, 1210, 1160, 1120, 1020, 950, 920, 890, 850, 810, 750 i 700 cm^{-1}.

[0062] Anal calcd. for $C_{24}H_{19}N_4O_2Cl_3$ (501.77 g/mol): C 57.44, H 3.81, and N 11.16. Found: C 57.38, H 3.62, and N 11.15%.

Example 9: *4-{2-[2-(6-methoxy-naphth-2-yl)-propionylamido]ethyl}amino-6-(3-triethoxysilylpropyl)amino-2,5-dichloro-1,3-dicyanobenzene and 4-{2-[2-(6-methoxy-naphth-2-yl)-propionylamido]ethyl}amino-2-(3-triethoxysilylpropyl) amino-5,6-dichloro-1,3-dicyanobenzene*

[0063] The compound prepared in Example 8 (0.7 g, 1.39 mmol) and 3-aminopropyltriethoxysilane (3.0 ml) are heated at 100°C bath temperature for 60 min. Purification by chromatography on silica gel column (35 g) with toluene as eluent afforded 0.92 g (96%) of the pure isomeric 1:1 product mixture.

[0064] IR (KBr): 3340, 2950, 2200, 1650, 1570, 1510, 1450, 1390, 1350, 1260, 1200, 1150, 1060, 960, 850 i 760 cm^{-1}.

[0065] Anal. calcd. for $C_{33}H_{41}O_5N_5Cl_2Si$ (686.68 $gmol^{-1}$): C 57.71, H 6.01, and N 10.20. Found: C 57.63, H 5.98, and N 10.28%.

Example 10: *Chiral stationary phase **FSC** 10*

[0066] A mixture of isomers (0.700 g; 1.01 mmol) as prepared in the Example 9 and

[0067] Nucleosil 100-5 (1.69 g) are heated under reflux in dry toluene (5 ml) for 20 h. The modified silica gel is filtered off, washed with cold toluene, and dried *in vacuo* at 70°C for 4 hr. 2 g of the chiral stationary phase ***FSC** 10* are obtained.

[0068] Anal. found: C 8.67%, H 1.77% eand N 1.26%. According to the elemental analysis it is calculated that 0.18 mmol of chiral selector is bound at 1 g of chiral stationary phase.

Example 11: *4-N-L-Asparagyl-2,5,6-trichloro-1,3-dicyanobenzene*

[0069] To the suspension of 2,4,5,6-tetrachloro-1,3-dicyanobenzene (5.0 g; 18.8 mmol) in methanol (100 ml) a pre-heated solution of L-asparagine monohydrate (5.64 g; 37.6 mmol) and sodium carbonate (3.98 g; 37.60 mmol) in water (100 ml) are added. The reaction mixture is heated at reflux for 1.5 h and filtered. The filtrate is washed with dichloromethane (2 x 100 ml), the aq. layer acidified with 1 M HCl (50 ml) and the acidic solution extracted with dichloromethane (2 x 100 ml). The organic phase is washed with water, filtered, concentrated to 100 ml. After storage in the refrigerator for 2 hr the solid product is precipitated and collected on G-4 filter. 2.51 g (37%) of title product as white solid material are obtained.

[0070] IR (KBr): 3480, 3360, 3320, 2900, 2500, 2220, 1730, 1650, 1570, 1500, 1400, 1320, 1200, 1120, 850, 810 cm^{-1}.

[0071] Anal, calcd. for $C_{12}H_7N_4O_3Cl_3$ (361.56): C 39.86, H 1.9, and N 15.49. Found: C 39.92, H 2.12, and N 15.41%.

Example 12: *Chiral stationary phase **FSC** 13*

[0072] The suspension of example 11 (0.55 g, 1.52 mmol), silica gel LiChrospher 100 NH_2 (1.96 g; 1.40 mmol of N2), and EEDQ (0.37 g; 1.52 mmol) in dry THF (10 ml) are stirred at room temperature for 16 h. The product is collected on G-4 filter, washed with methanol and dried at 70°C for 4 hr to afford 2.18 g of ***FSC** 13.*

[0073] Anal. found C 8.95%; H 1.43%; N 1.78%. According to %N it is calculated that 1.0 g of chiral stationary phase contains 0.14 mmol of chiral selector.

Example 13: *4-[L-prolinyl-L-alanilyl-(3,5-dimethylanilide)]-2,5,6-trichloro-1,3-dicyanobenzene*

[0074] N-Boc-L-alanine (2.77 g; 14.6 mmol) is transformed in 3,5-dimethylanilide by DCC (3.02 g, 14.6 mmol) promoted condensation with 3,5-dimethylaniline (1.77 g, 14.6 mmol), using dichloromethane as the solvent at ambient temperature. 1.78 g (63%) of the crude product are obtained. To 4-N-L-prolinyl-2,5,6-trichloro-1,3-dicyanobenzene (2.55 g; 7.4 mmol) dissolved in dichloromethane (15.0 ml) DCC (1.53 g, 7.4 mmol) in 10 ml dichloromethane is added, then a solution of 3,5-dimethylanilido-L-alanine (1.42 g; 7.4 mmol) in dichloromethane (15.0 ml). After 18 h stirring at ambient temperature the crude product is isolated on filtration on DC-urea and evaporation, then purified by chromatography on silica gel column using toluene-acetone (100:3) as eluent. It is obtained 1.95 g (50%) of the pure product as pale-yellow powder.

[0075] IR (KBr): 3380, 3300, 2980, 2920, 2880, 2220, 1660, 1610, 1550, 1520, 1440, 1350, 1260, 1210, 1170, 1140, 1060, 1000, 970, 920, 890, 840, 750, 730, 690 cm^{-1}.

Example 14: *4-[(L-prolinyl-L-alanilyl-(3,5-dimethylanilide)]-2,5-dichloro-6-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene, and 4-[L-prolinyl-L-alanilyl-(3,5-dimethylanilide)]-2,5-dichloro-2-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene*

[0076] The compound from Example 13 (0.81 g; 1.55 mmol) and 3-aminopropyltriethoxysilane (3.0 ml) are reacted and the pure product is isolated by purification on silica gel column (30 g) by elution with toluene-acetone (20:1). 0.79 g (72%) of the mixture of the title isomers (1:1) are obtained.

[0077] IR (KBr): 3360, 2980, 2920, 2880, 2200, 1650, 1610, 1570, 1520, 1450, 1390, 1350, 1300, 1260, 1220, 1160, 1080, 950, 840, 780 i 690 cm^{-1}.

Example 15: *Chiral stationary phase **FSC** 18*

[0078] A mixture of isomers from Example 14 (0.70 g, 1.0 mmol) and silica gel LiChrospher Si 100 (2.0 g, 10 mm) are heated under reflux of dry toluene for 20 h. The modified silica is collected on G-4 filter, is washed with toluene, then with 2-propanol, and n-hexane. On drying at 70°C for 4 h 1.94 g of ***FSC** 18* are obtained.

[0079] Elem. anal. found : C 5.78%, H 1.14% and N 1.92%, indicates that 1.0 g of CSP contains 0.109 mmol of the bound selector.

Example 16. *Stationary phase FS*

[0080] A mixture of Nucleosil 100-5 NH_2 (2.0 g, 3.49%C, 1.18%N, 1.94 mmol) and 2,4,5,6-tetrachloro-1,3-dicyanobenzene (1.0 g, 3.9 mmol) are heated in dry DMF (15.0 ml) at 100°C for 20 h. The product is collected on filter, washed with DMF, then with dichloromethane and with MeOH. On drying at 70°C for 4 h 1.2 g of stationary phase are obtained which has: Elem. anal. found : C 5.57%, H 1.07% and N 1.18%, indicates that 1.0 g of CSP contains 0.216 mmol of the bound material (based on C).

[0081] 2.17 g of said stationary phase is heated in 1,2-diaminoethane (10.0 ml) for 16 h at 90°C bath temperature. Product is collected on G-4 filter, is washed with 1m sodium carbonate, then methanol. On drying for 4 h at 70°C is obtained 2.12 g of stationary phase FS.

[0082] Elem. anal. found : C 6.19%, H 1.33% and N 1.24%, indicates that 1.0 g of CSP contains 0.021 mmol of the bound 1,2-diaminomethane (based on C).

Example 17: *Chiral stationary phase **FSC** 19*

[0083] To the suspension of FS of example 16 (2.0 g) in dry THF (20.0 ml) are added *N*-3,5-dinitrobenzoyl-L-leucine (1.9 g, 5.8 mmol) and EEDQ (1.44 g, 5.8 mmol). The reaction mixture is stirred for 16 h at ambient temperature, then ***FSC** 19* is isolated as previously described, affording 2.24 g of the product.

[0084] Elem. anal. found : C 12.98%, H 1.41% and N 1.71%, indicates that 1.0 g of CSP contains 0.434 mmol of the

bound DNB-Leu (based on C).

Example 18: *Chiral stationary phase **FSC** 20*

[0085] To the suspension of FS (2.0 g) in dry THF (20.0 ml) are added N-3,5-dinitrobenzoyl-L-phenylglycine (2.0 g, 5.82 mmol) and EEDQ (1.44 g, 5.8 mmol). The reaction mixture is stirred for 16 h at ambient temperature, then ***FSC** 20* isolated as previously described, affording 2.23 g of the product.

[0086] Elem. anal. found : C 12.58%, H 1.77% and N 2.09%, indicates that 1.0 g of CSP contains 0.354 mmol of the bound DNB-Phegly (based on C).

Example 19: *4-[(2-amino)cyclohexylamino]-2,5,6-trichloro-1,3-dicyanobenzene*

[0087] To the slurry of 2,4,5,6-tetrachloro-1,3-dicyanobenzene (2.0 g, 7.5 mmol) in acetonitrile (40 ml) triethylamine (5.0 ml) is added, then 1,2-diaminocyclohexane (0.86 g, 7.5 mmol) and the reaction mixture is heated under reflux for 1 h. It is cooled to ambient temperature, then deposited on ice for few hours, and the crystalline product is collected on filter. 2.32 g (89%) of the title product as pale-yellow powder are obtained.

[0088] IR (KBr): 3340, 3300, 3120, 2960, 2920, 2860, 2220, 1600, 1580, 1480, 1450, 1400, 1360, 1350, 1270, 1240, 1220, 1190, 1100, 1070, 1040, 990, 930, 900, 870, 850, 840, 740, 730 i 610 cm^{-1}.

[0089] Anal. calcd. for: $C_{14}H_{13}N_4Cl_3$ (343.63 g/mol): C 48.93, H 3.81, and N 16.30. Found: C 48.77, H 4.01, and N 16.35%.

Example 20: *4-/2-(3,5-dinitrobenzoyl)amide-cyclohexyl]amino-2,5,6-trichloro-1,3-dicyanobenzene*

[0090] To the solution of the compound obtained in Example 19 in THF (40 ml) triethylamine (1.0 ml) is added, then solution of 3,5-dinltrobenzoylchloride (0.68 g, 295 mmol) in THF (10 ml). After 1 h stirring at ambient temperature the solvent is evaporated in vacuo and the solid residue is slurried in methanol (50 ml). After 10 min sonification in an ultrasound bath the product is collected on filter, is washed with methanol and dried to afford 1.18 g (75%) of white powder.

[0091] IR (KBr): 3300, 3260, 3100, 2920, 2860, 2220, 1640, 1570, 1540, 1510, 1340, 1200, 1100, 1080, 920, 870, 850, 770, 750 i 720 cm^{-1}.

[0092] Anal. calcd. for: $C_{21}H_{15}N_6O_5Cl_3$ (537.73 g/mol): C 46.90, H 2.81, and N 15.63. Found: C 46.97, H 3.01, and N 15.52%.

Example 21: *4-{[2-(3,5-dinitrobenzoyl)-cyclohexyl]amide}-2,5-dichloro-6-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene, and 4-{[2-(3,5-dinitrobenzoyl)-cyciohexyl]amide)amino-5,6-dichloro-2-(3-triethoxysilylpropyl) amino-1,3-dicyanobenzene*

[0093] The compound from example 20 (1.0 g, 1.85. mmol) is dissolved in 3-aminopropyltriethoxysitane (5.0 ml) and DMF (1.0 ml) is added. Then the resulting solution is heated for 1 h at 100°C bath temperature. After evaporation *in vacuo,* the crude product is purified on silica gel column (30 g), by elution with toluene. It is obtained a re 1:1 mixture of the title isomers (1.27 g, 94%).

[0094] IR (KBr): 3420, 3100, 2980, 2920, 2880, 2210, 2200, 1600, 1590, 1500, 1500, 1450, 1390, 1340, 1220, 1190, 1160, 1100, 1080, 950, 780, 730, 720, 680 cm^{-1}.

[0095] Anal. calcd. for $C_{30}H_{38}N_7O_8Cl_2Si$ (723.64): C 49.78, H 5.29, and N 13.55. Found: C 50.03, H 5.75, and N 13.28%.

Example 22: *al Stationary phase **FSC** 22*

[0096] A mixture of isomers from example 21 (1.0 g, 1.35 mmol) and Nucleosil 100-5 (1.63 g) are heated for 20 h under reflux in dry toluene (15 ml). The product is collected on G-4 filter, washed first with toluene then with 2-propanol, and n-hexane. On drying at 70 °C for 4 h, 1.95 g of chiral stationary phase ***FSC*** 22 are obtained.

[0097] Elem. anal. found : C 7.98%, H 1.34% and N 1.26%, indicates that 1.0 g of FSC contains 0.128 mmol of the bound selector (based on C).

Example 23: *Chiral stationary phase **FSC** 24*

[0098] A suspension of FS prepared above (2.0 g), *N*-3,5-dinitrobenzoyl-L-phenylalanine (2.1 g; 5.8 mmol) and EEDQ (1.44 g; 5.8 mmol) in dry THF (20 ml) are stirred for 16 h at ambient temperature. The modified silica gel is collected

on G-4 filter, washed with methanol and dried at 70°C for 4 h to afford 2 g of ***FSC*** *24.*

Example 24: *Chiral stationary phase* ***FSC*** 25

[0099] Silicagel LiChrospher 100 NH_2 (2.0 g) is slurried in THF (10 ml), then 2,4,5,6-tetrachloro-1,3-dicyanobenzene (0.67 g, 2.5 mmol) and EEDQ (0.60 g, 2.5 mmol) are added. The reaction mixture is stirred for 16 h at ambient temperature. Then N-3,5-dinitrobenzoylamido-D-phenylglycine-(2-aminoethyl-(aminoethyl)-amide) (8.0 mmol) is added and stirring at 65°C is continued for 6 h. The resulting stationary phase ***FSC*** *25* is collected on filter, washed with methanol, and dried at 70 °C for 4h. It is obtained ca 3 g of ***FSC*** 25.

Example 25: *Chiral stationary phase* ***FSC*** *26*

[0100] Starting from silicagel Lichrospher 100 NH_2 (3.0 g) and 2,4,5,6-tetrachloro-1,3-dicyanobenzene (1.12 g, 4.2 mmol), and EEDQ (1.61 g, 6.5 mmol). The reaction mixture is stirred for 16 h at ambient temperature. Then N-3,5-dinitrobenzoylamido-D-phenylglycine-(*meta*-aminomethylphenyl)-methylamide (15.0 mmol) is added and stirring at 60 °C continued for 12 h. The resulting stationary phase is collected on filter, is washed with methanol, and dried at 70 °C for 4h. It is obtained 4.4 g of the stationary phase ***FSC*** *26*.

Example 26: *Chiral stationary phase* ***FSC*** *27*

[0101] Silicagel Lichrospher 100 NH_2 (3.0 g) and 2,4,5,6-tetrachloro-1,3-dicyanobenzene (1.06 g, 4.0 mmol), are slurried in tetrahydrofurane (20 ml), and EEDQ (1.48 g, 6.0 mmol) is added. The reaction mixture is stirred for 16 h at ambient temperature. Then *N*-3,5-dinitrobenzoylamido-D-phenylglycine-(*para*-aminomethylphenyl)methyl-amide (12.0 mmol) is added and stirring at 60°C continued for 8 h. The resulting stationary phase is collected on filter, is washed with methanol, and dried at 70 °C for 4h. 4.2 g of the stationary phase *FS 27* are obtained.

Example 27: *Chiral stationary phase* ***FSC*** *28*

[0102] Starting from silica gel Lichrospher 100 NH_2 (6.0 g) and 2,4,5,6-tetrachloro-1,3-dicyanobenzene (2.66 g, 10 mmol), and EEDQ (3.71 g, 15 mmol). The reaction mixture is stirred for 16 h at ambient temperature Then *N*-3,5-dinitrobenzoylamido-D-phenylglycine-(2-aminocyclohexyl)amide (35 mmol) is added and stirring at 60 °C continued for 10 h. The resulting stationary phase is collected on filter, is washed with methanol, and dried at 70 °C for 4h. 7.1 g of the ***FSC*** *28.* are obtained.

[0103] Chemical analysis of chiral selectors and chiral stationary phases prepared according to the present invention:

Example 28: *Chiral stationary phase* ***FSC*** *2*

[0104] Analysis, found; C 8.32, H 1.21, N 1.69 %. According to elemental analysis 0.17 mmol of the chiral selector is bound on 1.0 g of silica gel.

Example 29: *4-[(3,5-Dimethylanilido)-L-phenylalaninyl]-6-(3-triethoxysilyl)propylamino-2,5-dicloro-1,3-dicyanobenzene, and 4-[(3,5-dimethylanilido)-L-phenylalaninyl]-2-(3-triethoxysilyl)propylamino-5,6-dicloro, 1,3-dicyanobenzene*

[0105] IR (KBr): 3320, 3020, 2980, 2920, 2880, 2200, 1690, 1670, 1610, 1570, 1500, 1460, 1440, 1390,1360,1340, 1320, 1215, 1160, 1100, 950, 840, 790, 770, 740, 700,680 cm^{-1}.

[0106] Anal. calcd. for $C_{34}H_{41}N_5O_4Cl_2Si$ (682.69 g/mol): C 59.81, H 6.05 and N 10.26. Found: C 59.75, H 6.15 and N 10.29%.

Example 30: *4-[(Naphth-1-yl)amido)-L-phenylalaninyl]-2-(3-triethoxypropyl) amino-5,6-dichloro-1,3-dicyanobenzene and 4-[(Naphth-1-yl)amido)-L-phenylalaninyl]-6-(3-triethoxypropyl)amino-2,5-dichloro-1,3-dicyanobenzene*

[0107] IR (KBr): 3400, 3350, 3060, 3020, 2980, 2920, 2880, 2720, 2200, 2220, 1690, 1670, 1590, 1510, 1450, 1400, 1370, 1350, 1300, 1270, 1250, 1200, 1160, 1100, 1080, 950, 800, 770, 750, 700 cm^{-1}.

[0108] Analysis calcd. for: $C_{36}H_{39}N_5O_4Cl_2Si$ (704.70 g/mol): C 61.35, H 5.57 and N 9.94. Found: C 61.12, H 5.75 and N 9.98%.

Example 31: *Chiral stationary phase **FSC** 3*

[0109] Anal. found: C 8.99%, H 0.98%, N 1.58%. The % N reveals that 1.0 g of the stationary phase contains 0.23 mmol of chiral selector.

Example 32: *Chiral stationary phase **FSC** 4*

[0110] Anal. found: C 8.02%, H 1.03%, N 1.65%. The %N reveals that 1.0 g of the stationary phase contains 0.23 mmol of chiral selector.

Example 33: *4-[R-1-(naphth-1-yl)ethyl]amino-2-(3-triethoxysilylpropyl)amino-5,6-dichloro-1,3-dicyanobenzene and 4-[R-1-(naphth-1-yl)ethyl]amino-6-(3-triethoxysilylpropyl)amino-2,5-dichloro-1,3-dicyanobenzene*

[0111] IR (KBr): 3390, 3370, 2980, 2920, 2880, 2200, 1580, 1510, 1500, 1440, 1390, 1360, 1300, 1270, 1220, 1190, 1160, 1100, 1070, 950, 760, 700 cm^{-1}.

[0112] Anal. calcd. for $C_{29}H_{34}N_4SiO_3Cl_2$ (585.57 g/mol): C 59.47, H 5.85 and N 9.57%. Found: C 59.41, H 5.98, and N 9.55%.

Example 34: *Chiral stationary phase **FSC** 6*

[0113] Anal. found: C 6.51%, H 1.33%, N 1.23%. According to % of N it is calculated that 1.0 g of the stationary phase contains 0.22 mmol of chiral selector.

Example 35: *4-{n-butyl-[R-1-(naphth-1-yl)ethyl]acetamido}amino-6-(3-triethoxysilylpropyl)amino-2,5-dichloro-1,3-dicyanobenzene, and 4-{n-butyl-[R-1 (naphth-1-yl)ethyl]acetamido}amino-2-(3-triethoxysilylpropyl)amino-5,6-dichloro-1,3-dicyanobenzene*

[0114] IR (KBr): 3390, 3100, 2980, 2920, 2880, 2220, 1670, 1575, 1520, 1460, 1420, 1390, 1360, 1340, 1310, 1290, 1240, 1210, 1190, 1160, 1100, 1080, 950, 800, 780 cm^{-1}.

[0115] Anal. calcd. for $C_{35}H_{45}N_5SiO_4Cl_2$ (698.73 g/mol): C 60.15, H 6.49 and N 10.02. Found: C 60.27, H 6.57, and N 9.81%.

Example 36: *Chiral stationary phase **FSC** 7*

[0116] Analysis, found; C 7.16%, H 1.16%, N 1.78 %. According to elemental analysis. 0.25 mmol of the chiral selector is bound on 1.0 g of silica gel.

Example 37: *4-{n-butyl-[N-R-1-(cyclohexyl)ethyl-N-3,5-dinitrobenzyl]acetamido}amino-6-(3-triethoxysilylpropyl) amino-2,5-dichloro-1,3-dicyanobenzene and 4-{n-butyl-[N-R-1-(cyclohexyl)ethyl-N-3,5-dinitrobenzyl]acetamido} amino-2-(3-triethoxysilylpropyl)amino-5,6-dichloro-1,3-dicyanobenzene*

[0117] Anal. calcd. for $C_{38}H_{53}N_7SiO_8Cl_2$ (834.85 g/mol): C 54.66, H 6.39, and N 11.74. Found: C 54.73, H 6.28, and N 11.69.

Example 38: *Chiral stationary phase **FSC** 9*

[0118] Anal. found: C 6.69%, H 1.56%, and N 1.78%. According on % of nitrogen: 0.18 mmol of chiral selector is bound at 1 g of chiral stationary phase.

Example 39: *4-{methyl-[R-1-(naphth-1-yl)ethyl]acetamido}amino-2-(3-triethoxysilylpropyl)amino-5,6-dichloro-1,3-dicyanobenzene, and 4-{methyl-[R-1-(nephth-1-yl)ethyl]acetamido}amino-6-(3-Triethoxysilylpropyl)amino-2, 5-dichloro-1,3-dicyanobenzene*

[0119] IR (KBr): 3380, 2980, 2920, 2880, 2200, 1670, 1580, 1510, 1450, 1390, 1360, 1300, 1220, 1160, 1100, 950, 780 cm-1.

[0120] Anal. calcd. for $C_{32}H_{39}N_5SiO_4Cl_2$ (656.66): C 58.52, H 5.98, and N 10.66. Found: C 58.48, H 6.12, and N 10.77%.

Example 40: *Chiral stationary phase **FSC** 11*

[0121] Anal. found C 6.60%, H 0.95% and N 1.27%. On the basis of nitrogen: 1.0 g of chiral stationary phase contain 0.18 mmol of chiral selector.

Example 41: *Chiral stationary phase **FSC** 12*

[0122] Anal. found. C 8.83%, H 1.38% and N 1.71%. On the basis of %N it is calculated that 1.0 g of chiral stationary phase contain 0.17 mmol of chiral selector.

Example 42: *4-[3,5-dimethylanilido)-L-alaninyl]-2,5-dichloro-6-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene, and 4-[3,5-dimethylanilido)-L-alaninyl]-5,6-dichloro-2-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene*

[0123] IR (KBr): 3325, 2980, 2920, 2880, 2200, 1680, 1610, 1590, 1510, 1450, 1390, 1200, 1160, 1100, 1080, 950, 840, 780, 690 cm^{-1}.

[0124] Anal. calcd. for $C_{28}H_{37}N_5O_4Cl_2Si$ (606.61): C 55.43, H 6.14, and N 11.54. Found: C 55.25, H 6.16, and N 11.82%.

Example 43: *Chiral stationary phase **FSC** 14*

[0125] Anal. found C 6.42%, H 1.14%, N 1.52%. On the basis of %N it is calculated that 1.0 g of stationary phase contains 0.22 mmol of chiral selector.

Example 44: *4-(cyclohexylamido-L-alaninyl)-2,5-dichloro-6-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene, and 4-(cyclohexylamido-L-alaninyl)-5,6-dichloro-2-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene*

[0126] IR (KBr): 3330, 2980, 2920, 2210, 1660, 1580, 1500, 1450, 1390, 1360, 1350, 1310, 1290, 1250, 1220,1200, 1160, 1100, 1070, 950, 890, 770 cm^{-1}.

[0127] Anal. calcd. for $C_{26}H_{39}N_5O_4Cl_2Si$ (584.60): C 53.41, H 6.72, and N 11.98. Found: C 53.18, H 6.59, and N 11.79%.

Example 45: *Chiral stationary phase **FSC** 15*

[0128] Anal. found C 7.00%, H 1.37% and N 1.49%. On the basis of %N it is calculated that 1.0 g of chiral stationary phase contains 0.21 mmol of chiral selector.

Example 56: *4-[(3,5-dimethylanilido)-prolinyl]-2,5-dichloro-6-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene, and 4-[(3,5-dimethylanilido)-prolinyl]-5,6-Dichloro-2-(3-triethoxysilylpropyl)amino1,3-dicyanobenzene*

[0129] IR (KBr): 3330, 2990, 2960, 2940, 2200, 1680, 1610, 1580, 1530, 1450, 1390, 1350, 1300, 1200, 1160, 1000, 950, 840, 780, 690 cm^{-1}.

[0130] Elem. anal. calcd. for $C_{30}H_{39}N_5O_4Cl_2Si$ (632.64): C 56.95, H 6.21, and N 11.07. Found: C 57.12, H 5.96, and N 11.02%.

Example 47: *Chiral stationary phase **FSC** 16*

[0131] Anal. found : C 8.01%, H 1.91% and N 1.72%, indicates that 1.0 g of CSP contains 0.25 mmol of the bound selector.

Example 48: *4-(prolinyl-cyclohexylamide)-2,5-dichloro-6-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene, and 4-(prolinyl-cyclohexylamide)-5,6-dichloro-2-(3-triethoxysilylpropyl)amino-1,3-dicyanobenzene*

[0132] IR (KBr): 3440, 2990, 2960, 2940, 2200, 1660, 1580, 1520, 1470, 1450, 1390, 1350, 1300, 1200, 1190, 1160, 1100, 1080, 950, 780 cm^{-1}.

[0133] Anal. calcd. for $C_{28}H_{41}N_5O_4Cl_2Si$ (610.64): C 55.06, H 6.76, and N 11.47. Found: C 55.18, H 6.38, and N 11.30%.

Example 49: *Chiral stationary phase **FSC** 17*

[0134] Elem. anal. found : C 7.42%, H 1.67% and N 1.63%, indicates that 1.0 g of CSP contains 0.23 mmol of the bound selector.

Example 50: *4-{2-[2-(6-methoxy-naphth-2-yl)-propionylamido]cyclohexyl}amino-6-(3-triethoxysilylpropyl)amino-2,5-dichloro-1,3-dicyanobenzene and 4-{2-[2-(6-methoxy-naphth-2-yl)-propionylamido]cyclohexyl}amino-2-(3-triethoxysilylpropyl)amino-5,6-dichloro-1,3-dicyanobenzene*

[0135] IR (KBr): 3350, 2940, 2200, 1650, 1580, 1510, 1450, 1390, 1350, 1260, 1200, 1160, 1070, 950, 850 i 770 cm^{-1}.
[0136] Anal. calcd. for $C_{37}H_{48}N_5O_5Cl_2Si$ (741.78 g/mol): C 59.90, H 6.52, and N 9.44. Found: C 60.04, H 6.48, and N 9.37%.

Example 51: *Chiral stationary phase **FSC** 23*

[0137] Elem. anal. found : C 7.98%, H 1.34% and N 1.26%, indicates that 1.0 g of CSP contains 0.172 mmol of the bound chiral selector (based on N).

[0138] Examples of resolution of racemates with chiral stationary phases according to the present invention

Example 52: *Resolution of racemate with **FSC***

[0139] Chromatographic column for HPLC is filled with ***FSC*** and several racemic mixtures were separated using n-hexane/2-propanol (9:1) as eluent. Two enantiomers for each of mixture tested were resolved as completely separated symmetric peaks with Rt_1 and Rt_2 given in table 1 (Rt_1 and Rt_2 mean the retention time for each peak, in minutes):

TABLE 1

		Rt_1	Rt_2
***FSC** 10*	TR19	9.53	13.52
***FSC** 8*	TR22	5.50	8.00
***FSC** 7*	TR17	11.1	20.1

Example 53 *Chromatographic separation of racemates with FSC*

[0140] A number of racemic mixtures are employed as analytes to evaluate the chromatographic performance of several ***FSC.*** The eluent used is either n-hexane / 2-propanol (9 : 1) (A) or n-hexane / dichloromethane / methanol (100 : 30 : 1) (B). The results are reported in Table 2.

TABLE 2: Separation of several racemic analytes listed in Figure 6 with the stationary phases of the invention. The letter in brackets refers to the eluent used.

racemic analyte												
TR17	***FSC** 10* (A)			***FSC** 8* (A)			***FSC** 18* (A)			***FSC** 13* (A)		
	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S
	6.10	8.59	2.62	3.96	5.17	2.45	2.64	8.75	13.41	3.81	3.93	0.21
TR19	***FSC** 11* (A)			***FSC** 7* (A)			***FSC** 10* (A)			***FSC** 18* (A)		
	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S
	5.19	10.89	7.29	3.91	7.74	5.28	3.96	6.04	3.98	1.29	6.60	17.97
TR23	***FSC** 3* (B)			***FSC** 7* (A)			***FSC** 8* (A)			***FSC** 18* (A)		
	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S
	2.61	3.57	3.37	8.43	17.8	6.31	5.09	7.26	6.25	3.06	10.26	3.77
TR6	***FSC** 1* (A)			***FSC** 5* (A)			***FSC** 13* (A)			***FSC** 20* (A)		
	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S
	2.08	2.18	0.50	2.99	3.25	0.72	1.31	1.41	0.69	1.51	1.79	0.58

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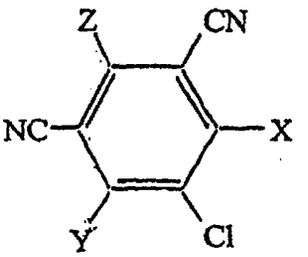
cont'd

TABLE 2: Separation of several racemic analytes listed in Figure 6 with the stationary phases of the invention. The letter in brackets refers to the eluent used.

racemic analyte												
TR8	***FSC** 1* (B)			***FSC** 13* (B)			***FSC** 12* (B)			***FSC** 20* (A)		
	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S
	2.03	2.16	0.84	4.84	5.08	0.78	3.54	3.82	1.02	11.46	14.53	0.72
TR9	***FSC** 11* (B)			***FSC** 12* (A)			***FSC** 4* (A)			***FSC** 19* (A)		
	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S
	2.52	2.65	0.55	1.62	1.76	0.58	1.06	1.22	0.34	2.89	3.53	0.37
TR15	***FSC** 11* (A)			***FSC** 7* (A)			***FSC** 3* (A)			***FSC** 12* (A)		
	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S	k'_1	k'_2	R_S
	1.40	1.56	0.84	0.26	0.28	0.89	0.25	0.44	1.31	2.77	2.95	0.82

Claims

1. Chiral selector of formula (I)



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wherein:

X=NR_1-CHR_2R_3
R_1 is selected from: H, alkyl C_1-C_6 linear or branched,
R_2 is selected from: H, alkyl C_1-C_6 linear or branched, aryl or arylalkyl possibly containing an heteroatom, said aryl or arylalkyl being optionally substituted with - OH, or -CH_2CONH_2,
R_3 is selected from: alkyl C_1-C_6 linear or branched, $(CH_2)_p$-COOH, $(CH_2)_p$-$CONH_2$, $(CH_2)_p$-$CONHR_4$, $(CH_2)_p$-$NHCOR_4$,$(CH_2)_p$-$CON(R_4R_5)$,$CONHCH(R_4)CONHR_4$,$(CH_2)_p$-$NHCOCH(R_4)NHCOR_4$,C_6H_4-CH_2-NH-$COCH(R_4)NHCOR_4$, $CH_2NH(CH_2)_p$-$NHCOCH(R_4)NHCOR_4$, where p is an integer from 0 to 4, R_4 and R_5 independently of each other are selected from:

(a) alkyl C_1-C_6 linear or cyclic,
(b) aryl,
(c) a spacer group of formula -$(CH_2)_n$-Si-$(OR_6)_3$ where n is comprised between 1 and 10 and R_6 is an alkyl C_1-C_4;

said groups (a) and (b) being optionally substituted with alkyl C_1-C_4, aryl, cycloalkyl C_5-C_6, NO_2, OCH_3, or:

(i) R_1 forms together with R_2, with the carbon atom bound to R_2 and with the nitrogen, a 5-6 membered ring, or
(ii) R_2 forms with R_3 and with the carbon atom bound to R_2 and R_3 a 5-6 membered ring substituted by -$NHCOR_4$, or by -$NHCOCH(R_4)NHCOR_4$, R_4 being as above defined;

Y e **Z** independently of each other are selected from: chloro, X group where X has the meanings given above, a spacer group of formula -$A(CH_2)_n$-Si-$(OR_6)_3$ where A represents NH or O, and n and R_6 have the meanings given above; with the proviso that said formula (I) contains: (a) one to three X groups containing at least one chiral atom, and (b) only one spacer group as above defined.

2. Chiral selector according to claim 1, wherein:

R_1 is selected from H, alkyl C_1-C_6 linear or branched, R_2 is selected from H, alkyl C_1-C_6 linear or branched, aryl, arylalkyl, CH_2CONH_2, or R_1 forms with R_2, with the carbon atom bound to R_2 and with N a 5-6 membered ring; R_3 is selected from alkyl C_1-C_6 linear or branched, $(CH_2)_p$-$CONHR_4$, $(CH_2)_p$-$CON(R_4R_5)$, where p, R_4 and R_5 have the meanings given above.

3. Chiral selector according to claim 1, wherein:

R_1 is H, R_2 is H, R_3 is selected from $(CH_2)_p$-$NHCOR_4$, CH_2-$NHCOR_4$, where p, R_4 have the meanings given above; or R_2 forms with R_3 and the carbon atom bound to R_2 and R_3 a 5-6 membered ring.

4. Chiral selector according to claim 1, wherein:

R_1 is H, , R_2 is H, or R_2 forms with R_1, with the carbon atom bound to R_2 and with
N a 5-6 membered ring; R_3 is $CONHCH(R_4)CONHR_4$, where p, R_4 have the meanings given above.

5. Chiral selector according to claim 1, wherein:

R_1 is H, R_2 is H, R_3 is selected from: $(CH_2)_p$-$NHCOCH(R_4)NHCOR_4$, C_6H_4-CH_2-$NHCOCH(R_4)NHCOR_4$, $CH_2NH(CH_2)_p$-$NHCOCH(R_4)NHCOR_4$; or R2 forms with R3 and with the carbon atom bound to R2 and R3 a 5-6 membered ring substituted with $NHCOCH(R_4)NHCOR_4$; p and R_4 having the meanings given above.

6. Chiral stationary phase for chromatography comprising a compound of formula (I) of claim 1.

7. Chiral stationary phase according to claim 6, wherein the solid support is chosen among silica, silica gel, alumina, kaolin, titanium oxide, magnesium, silicate, synthetic polymers.

8. Process for the preparation of chiral stationary phases of claim 6, involving the use of 1,3-dicyano-2,4,5,6-tetrachlorobenzene as a reagent, and comprising the following separate reaction steps which can take place in any order:

- introduction of one or more chiral groups X on the 1,3-dicyanobenzene ring, said X group having the structure defined in claim 1.
- introduction of the spacer group either on 1,3-dicyanobenzene ring, or on a X chiral group already present on the 1,3-dicyanobenzene ring, said spacer group having the structure defined in claim 1,
- formation of covalent linkage between the spacer group and a solid support.

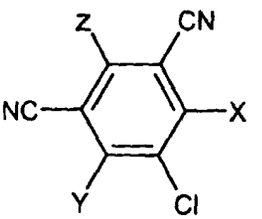
9. Process according to claim 8, wherein the X groups are introduced on the 1,3-dicyano benzene ring by using a reagent chosen among 1-phenylethylamine, proline, (l-(naphth-1-yl)ethylamine, phenylalanine, phenylglycine, n-butylamine, naphthylethylamine, 3,5-dimethylaniline, cyclohexylethylamine, sarcosine, asparagine.

10. Use of chiral stationary phases according to claims 6-7 in the analytical or preparative chromatographic separation of enantiomers or mixture of racemates.

11. Use according to claim 10, wherein the separation is carried out by means of high performance liquid chromatography (HPLC).

Patentansprüche

1. Ein chiraler Selektor der Formel (I)



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wobei:

$X = NR_1$-CHR_2R_3
R_1 wird ausgewählt aus: H, linearen oder verzweigten C_1-C_6-Alkylgruppen,
R_2 wird ausgewählt aus: H, linearen oder verzweigten C_1-C_6-Alkylgruppen, Aryl- oder Arylalkylgruppen, gegebenenfalls mit einem Heteroatom, wobei die Aryl- oder Arylalkylgruppe mit -OH oder $-CH_2CONH_2$ substituiert sein kann,

R_3 wird ausgewählt aus: linearen oder verzweigten C_1-C_6-Alkylgruppen, $(CH_2)_p$-COOH, $(CH_2)_p$-$CONH_2$, $(CH_2)_p$-$CONHR_4$, $(CH_2)_p$-$NHCOR_4$, $(CH_2)_p$-$CON(R_4R_5)$, $CONHCH(R_4)$, $CONHR_4$, $(CH_2)_p$-$NHCOCH(R_4)NHCOR_4$, C_6H_4-CH_2-$NHCOCH(R_4)NHCOR_4$, $CH_2NH(CH_2)_p$-$NHCOCH(R_4)NHCOR_4$, wobei p eine ganze Zahl zwischen 0 und 4 ist und R_4 und R_5 unabhängig voneinander ausgewählt werden aus:

(a) linearen oder cyclischen C_1-C_6-Alkylgruppen
(b) Arylgruppen
(c) einer Abstandshaltergruppe (Spacer) der Formel $-(CH_2)_n$-Si-$(OR_6)_3$, wobei n zwischen 1 und 10 beträgt und R_6 eine C_1-C_4-Alkylgruppe ist;

die Gruppen (a) und (b) können mit C_1-C_4-Alkyl-, Aryl-, C_5-C_6-Cycloalkyl-, NO_2- oder OCH_3-Gruppen substituiert sein;
oder:

(i) R_1 bildet zusammen mit R_2, mit dem an R_2 gebundenen Kohlenstoffatom und mit dem Stickstoffatom einen 5- oder 6-gliedrigen Ring, oder
(ii) R_2 bildet mit R_3 und mit dem an R_2 und R_3 gebundenen Kohlenstoffatom einen 5-oder 6-gliedrigen Ring, welcher durch $-NHCOR_4$ substituiert ist oder durch $-NHCO-CH(R_4)NHCOR_4$, wobei R_4 wie oben definiert ist;

Y und Z werden unabhängig von einander ausgewählt aus: Chlor, der Gruppe X, wobei X die oben genannte Bedeutung hat, einer Abstandshaltergruppe (Spacer) der Formel - $A(CH_2)_n$-Si-$(OR_6)_3$, wobei A NH oder O darstellt und n und R_6 die oben genannte Bedeutung haben;

unter der Bedingung, dass die Formel (I) enthält: (a) ein bis drei X-Gruppen mit mindestens einem chiralen Atom, und (b) nur eine wie oben beschriebene Abstandshaltergruppe (Spacer).

2. Ein chiraler Selektor gemäß Anspruch 1, wobei
R_1 ausgewählt wird aus H- oder linearen oder verzweigten C_1-C_6-Alkylgruppen, R_2 ausgewählt wird aus H-, linearen oder verzweigten C_1-C_6-Alkylgruppen, Aryl- oder Arylalkylgruppen oder $-CH_2CONH_2$, oder R_1 mit R_2 und mit dem an R_2 gebundenen Kohlenstoffatom und mit dem Stickstoffatom einen 5- oder 6-gliedrigen Ring bildet, und R_3 ausgewählt wird aus linearen oder verzweigten C_1-C_6-Alkylgruppen, $(CH_2)_p$-$CONHR_4$, $(CH_2)_p$-$CON(R_4R_5)$, wobei p, R_4 und R_5 die oben genannte Bedeutung haben.

3. Ein chiraler Selektor gemäß Anspruch 1, wobei
R_1 H ist, R_2 H ist und R_3 ausgewählt wird aus $(CH_2)_p$-$NHCOR_4$, oder CH_2-$NHCOR_4$, wobei p und R_4 die oben genannte Bedeutung haben; oder R_2 mit R_3 und mit dem an R_2 und R_3 gebundenen Kohlenstoffatom einen 5- oder 6-gliedrigen Ring bildet.

4. Ein chiraler Selektor gemäß Anspruch 1, wobei
R_1 H ist, R_2 H ist, oder R_2 zusammen mit R_1, mit dem an R_2 gebundenen Kohlenstoffatom und mit dem Stickstoffatom einen 5- oder 6-gliedrigen Ring bildet; und R_3 $CONHCH(R_4)CONHR_4$ ist, wobei p und R_4 die oben genannte Bedeutung haben.

5. Ein chiraler Selektor gemäß Anspruch 1, wobei
R_1 H ist, R_2 H ist, und R_3 ausgewählt wird aus$(CH_2)_p$-$NHCOCH(R_4)NHCOR_4$, C_6H_4-CH_2-$NHCOCH(R_4)NHCOR_4$, $CH_2NH(CH_2)_p$-$NHCOCH(R_4)NHCOR_4$, oder R_2 mit R_3 und mit dem an R_2 und R_3 gebundenen Kohlenstoffatom einen 5- oder 6-gliedrigen Ring bildet, der mit $NHCOCH(R_4)NHCOR_4$ substituiert ist, wobei p und R_4 die oben genannte Bedeutung haben.

6. Eine chirale stationäre Phase für die Chromatographie, welche eine Verbindung der Formel (I) gemäß Anspruch 1 enthält.

7. Eine chirale stationäre Phase gemäß Anspruch 6, wobei der feste Träger ausgewählt wird aus Siliciumdioxid, Silicagel, Aluminiumoxid, Kaolin, Titanoxid, Magnesium, Silikat oder synthetischen Polymeren.

8. Verfahren zur Herstellung von chiralen stationären Phasen gemäß Anspruch 6, welcher die Verwendung von 1,3-Dicyano-2,4,5,6-tetrachlorbenzol als ein Reagenz beinhaltet und die folgenden getrennten Reaktionsschritte

umfaßt, die in jedweder Reihenfolge ausgeführt werden können:

- Einführung einer oder mehrerer chiraler Gruppen X am 1,3-Dicyanobenzolring, wobei die X-Gruppe eine Struktur gemäß Anspruch 1 aufweist.
- Einführung der Abstandshaltergruppe (Spacer) entweder am 1,3-Dicyanobenzolring oder an einer chiralen, bereits am 1,3-Dicyanobenzolring befindlichen X-Gruppe, wobei die Abstandshaltergruppe (Spacer) eine Struktur gemäß Anspruch 1 aufweist.
- Bildung einer kovalenten Bindung zwischen der Abstandshaltergruppe (Spacer) und dem festen Träger.

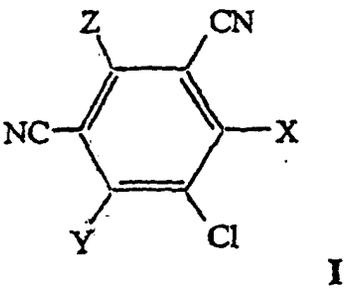
9. Verfahren gemäß Anspruch 8, wobei die X-Gruppen am 1,3-Dicyanobenzolring mittels eines Reagens eingeführt werden, welches ausgewählt wird aus 1-Phenylethylamin, Prolin, 1-1-(1-Napthyl)ethylamin, Phenylalanin, Phenylglycin, n-Butylamin, Naphtylethylamin, 3,5-Dimethylanilin, Cyclohexylethylamin, Sarkosin oder Asparagin.

10. Verwendung der chiralen stationären Phase gemäß der Ansprüche 6 oder 7 in der analytischen oder präparativen chromatischen Trennung von Enantiomeren oder Racematmischungen.

11. Verwendung gemäß Anspruch 10, wobei die Trennung mittels Hochleistungsflüssigkeitschromatographie (HPLC) ausgeführt wird.

Revendications

1. Sélecteur chiral de formule (I):



I

dans laquelle :

- **X** représente un groupe NR_1-CHR_2R_3,
- **R_1** est choisi parmi H, les groupes alkyle C_1-C_6 linéaires ou ramifiés,
- **R_2** est choisi parmi H, les groupes alkyle C_1-C_6 linéaires ou ramifiés, aryle ou arylalkyle contenant éventuellement un hétéroatome, ledit groupe aryle ou arylalkyle étant éventuellement substitué par OH ou par -CH_2CONH_2,
- **R_3** est choisi parmi les groupes alkyle C_1-C_6 linéaires ou ramifiés, $(CH_2)_p$-COOH, $(CH_2)_p$-$CONH_2$, $(CH_2)_p$-$CONHR_4$, $(CH_2)_p$-$NHCOR_4$, $(CH_2)_p$-$CON(R_4R_5)$, $CONHCH(R_4)CONHR_4$, $(CH_2)_p$-$NHCOCH(R_4)NH$-COR_4, C_6H_4-$CH_2NHCOCH(R_4)NHCOR_4$, $CH_2NH(CH_2)_pNHCOCH(R_4)$-$NHCOR_4$, où p est un nombre entier variant de 0 à 4, R_4 et R_5, indépendamment l'un de l'autre, sont choisis entre:

- (a) un groupe allyle C_1-C_6 linéaire ou cyclique,
- (b) un groupe aryle,
- (c) un groupe espaceur de formule -$(CH_2)_n$-Si-$(OR_6)_3$ dans laquelle n est compris entre 1 et 10 et R_6 représente un groupe alkyle C_1-C_4,

lesdits groupes (a) et (b) étant éventuellement substitués par des groupes alkyle C_1-C_4, aryle, cycloalkyle C_5-C_6, NO_2, OCH_3,
ou :

- (i) R_1 forme en association avec R_2, avec l'atome de carbone lié à R_2 et avec l'atome d'azote, un cycle à 5 ou

6 atomes, ou

- (ii) R_2 forme avec R_3 et avec l'atome de carbone lié à R_2 et R_3, un cycle à 5 ou 6 atomes substitué par $-NHCOR_4$ ou par $-NHCOCH(R_4)NHCOR_4$, R_4 étant tel que défini plus haut ;
- Y et Z, indépendamment l'un de l'autre, sont choisis entre les groupes chloro, le groupe X où X est tel que défini plus haut, un groupe espaceur de formule $-A(CH_2)_n-Si-(OR_6)_3$ dans laquelle A représente NH ou O, et n et R_6 sont tels que définis plus haut ; à la condition que ladite formule (I) contienne : (a) un à trois groupes X contenant au moins un atome chiral, et (b) seulement un groupe espaceur tel que défini plus haut.

2. Sélecteur chiral selon la revendication 1, dans lequel :

- R_1 est choisi entre H, un groupe alkyle C_1-C_6 linéaire ou ramifié,
- R_2 est choisi entre H, un groupe alkyle C_1-C_6 linéaire ou ramifié, aryle, arylalkyle, CH_2CONH_2, ou R_1 forme avec R_2, avec l'atome de carbone lié à R_2 et avec N, un cycle à 5 ou 6 atomes ;
- R_3 est choisi entre un groupe alkyle C_1-C_6 linéaire ou ramifié, un groupe $(CH_2)_p-CONHR_4$, un groupe $(CH_2)_p-CON(R_4R_5)$ où p, R_4 et R_5 sont tels que définis plus haut.

3. Sélecteur chiral selon la revendication 1, dans lequel :

R_1 représente H, R_2 représente H, R_3 est choisi entre $(CH_2)_p-NHCOR_4$, $CH_2-NHCOR_4$ où p et R_4 sont tels que définis plus haut ; ou R_2 forme avec R_3 et avec l'atome de carbone lié à R_2 et R_3 un cycle à 5 ou 6 atomes.

4. Sélecteur chiral selon la revendication 1, dans lequel :

R_1 représente H, R_2 représente H ou R_2 forme avec R_1, avec l'atome de carbone lié à R_2 et avec N, un cycle à 5 ou 6 atomes ; R_3 représente $CONHCH(R_4)CONHR_4$ où p et R_4 sont tels que définis plus haut.

5. Sélecteur chiral selon la revendication 1, dans lequel :

R_1 représente H, R_2 représente H, R_3 est choisi entre $(CH_2)_p-NHCOCH-(R_4)NHCOR_4$, $C_6H_4-CH_2NHCOCH(R_4)NHCOR_4$, $CH_2NH-(CH_2)_pNH-COCH(R_4)NHCOR_4$; ou R_2 forme avec R_3 et avec l'atome de carbone lié à R_2 et R_3, un cycle à 5 ou 6 atomes substitué par $NHCOCH(R_4)-NHCOR_4$; p et R_4 étant tels que définis plus haut.

6. Phase stationnaire chirale pour chromatographie, comprenant un composé de formule (I) selon la revendication 1.

7. Phase stationnaire chirale selon la revendication 6, dans laquelle le support solide est choisi parmi la silice, le gel de silice, l'alumine, le kaolin, l'oxyde de titane, le silicate, le magnésium, les polymères synthétiques.

8. Procédé pour la préparation de phases stationnaires chirales selon la revendication 6, impliquant l'utilisation de 1,3-dicyano-2,4,5,6-tétrachlorobenzène en tant que réactif, et comprenant les étapes réactionnelles séparées suivantes qui peuvent se dérouler dans n'importe quel ordre :

- introduction d'un ou plusieurs groupes chiraux X sur le cycle 1,3-dicyanobenzène, ledit groupe X ayant la structure définie dans la revendication 1 ;
- introduction du groupe espaceur, soit sur le cycle 1,3-dicyanobenzène, soit dans un groupe chiral X déjà présent sur le cycle 1,3-dicyanobenzène, ledit groupe espaceur ayant la structure définie dans la revendication 1.
- formation de liaison covalente entre le groupe espaceur et un support solide.

9. Procédé selon la revendication 8, dans lequel les groupes X sont introduits sur le cycle 1,3-dicyanobenzène en utilisant un réactif choisi parmi la 1-phényléthylamine, la proline, le 1-(napht-1-yl)éthylamine, la phénylalanine, la phénylglycine, la n-butylamine, la naphtyléthylamine, la 3,5-diméthylaniline, la cyclohexyléthylamine, la sarcosine, l'asparagine.

10. Utilisation de phases stationnaires chirales selon la revendication 6 et la revendication 7, dans la séparation chromatographique analytique ou préparative d'énantiomères ou de mélange de racémates.

11. Utilisation selon la revendication 10, dans laquelle la séparation est effectuée par chromatographie liquide haute

performance (HPLC).

Figure 1

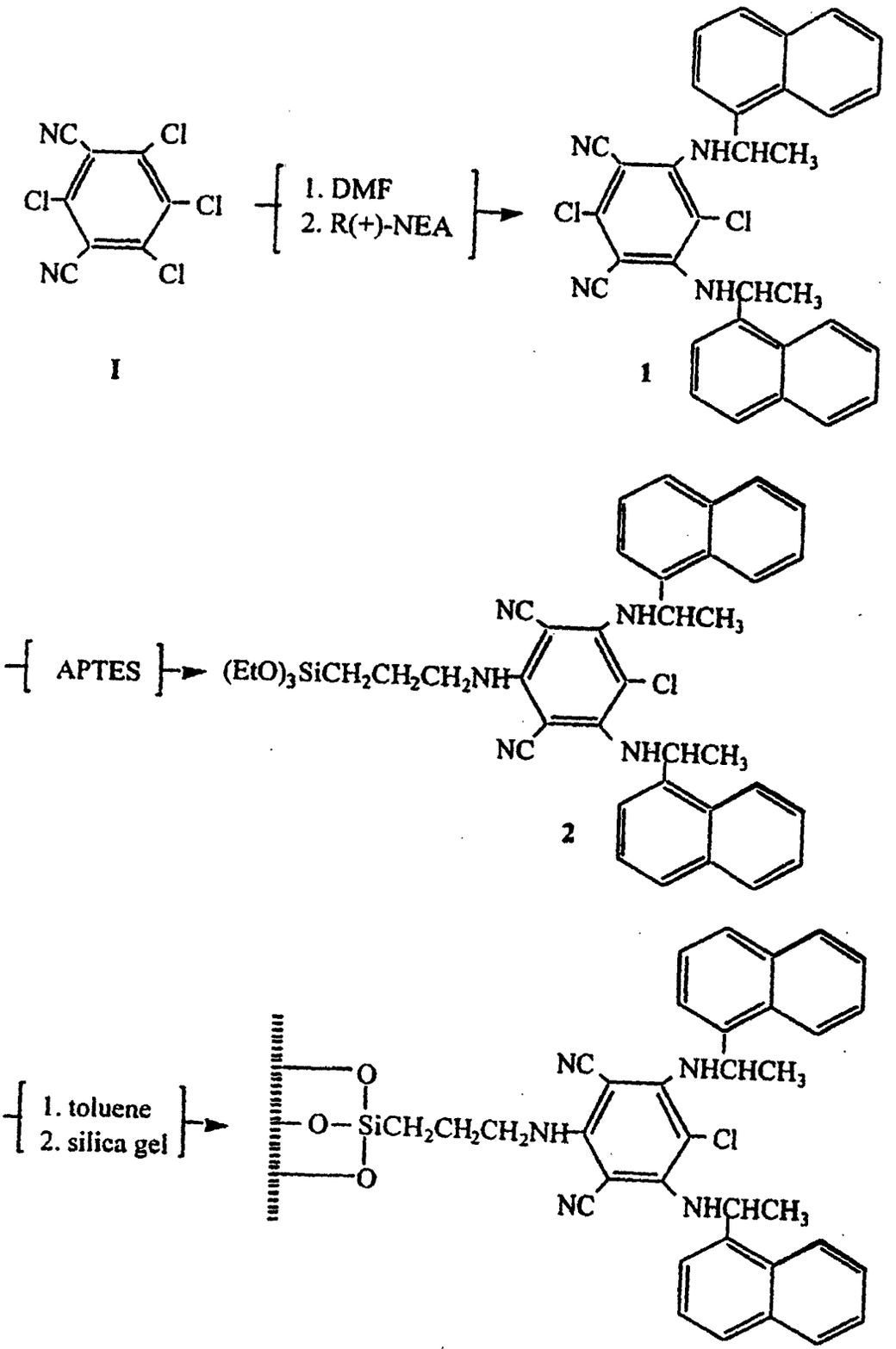

NC
Cl
Cl
Cl
NC
Cl
1. DMF
2. R(+)-NEA
NC
NHCHCH3
Cl
Cl
NC
NHCHCH3
I
1
APTES
(EtO)3SiCH2CH2CH2NH
NC
NHCHCH3
Cl
NC
NHCHCH3
2
1. toluene
2. silica gel
O
O
O
SiCH2CH2CH2NH
NC
NHCHCH3
Cl
NC
NHCHCH3

Figure 2

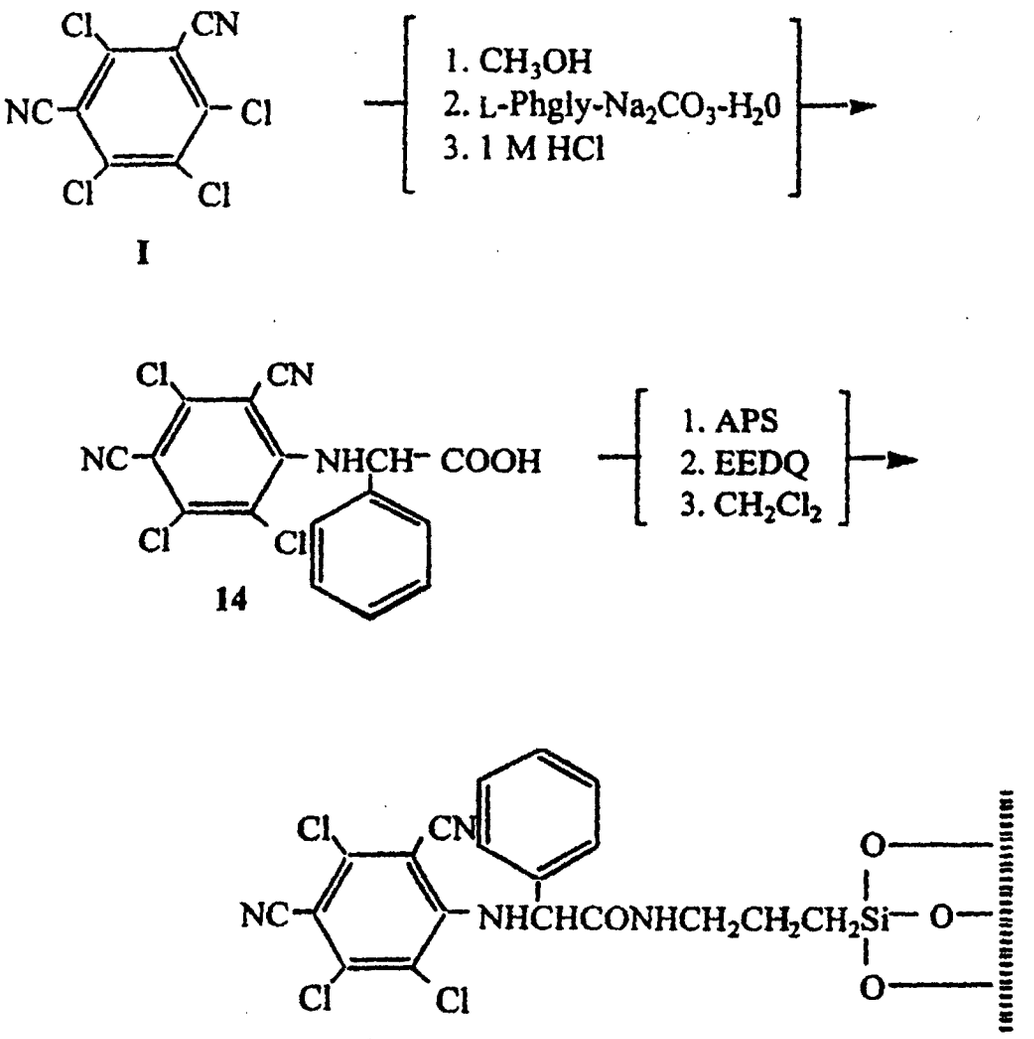

Cl
CN
NC
Cl
Cl
Cl
1. CH3OH
2. L-Phgly-Na2CO3-H20
3. 1 M HCl
I
NHCH- COOH
1. APS
2. EEDQ
3. CH2Cl2
14
NHCHCONHCH2CH2CH2Si
O

Figure 3

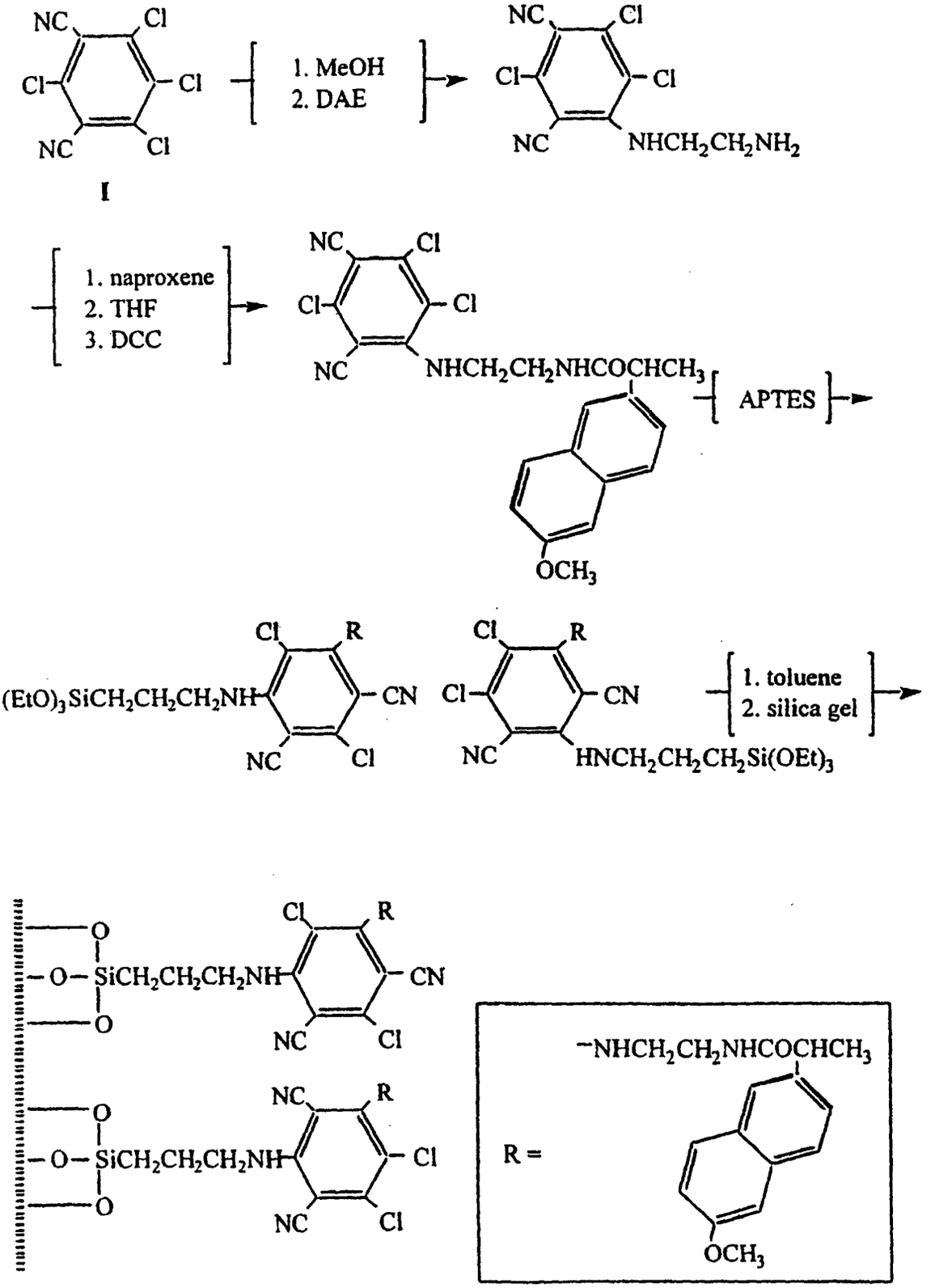

NC
Cl
Cl
Cl
NC
Cl
I
1. MeOH
2. DAE
NHCH2CH2NH2
1. naproxene
2. THF
3. DCC
NHCH2CH2NHCOCHCH3
APTES
OCH3
(EtO)3SiCH2CH2CH2NH
R
CN
1. toluene
2. silica gel
HNCH2CH2CH2Si(OEt)3
O
SiCH2CH2CH2NH
–NHCH2CH2NHCOCHCH3
R =

Figure 4

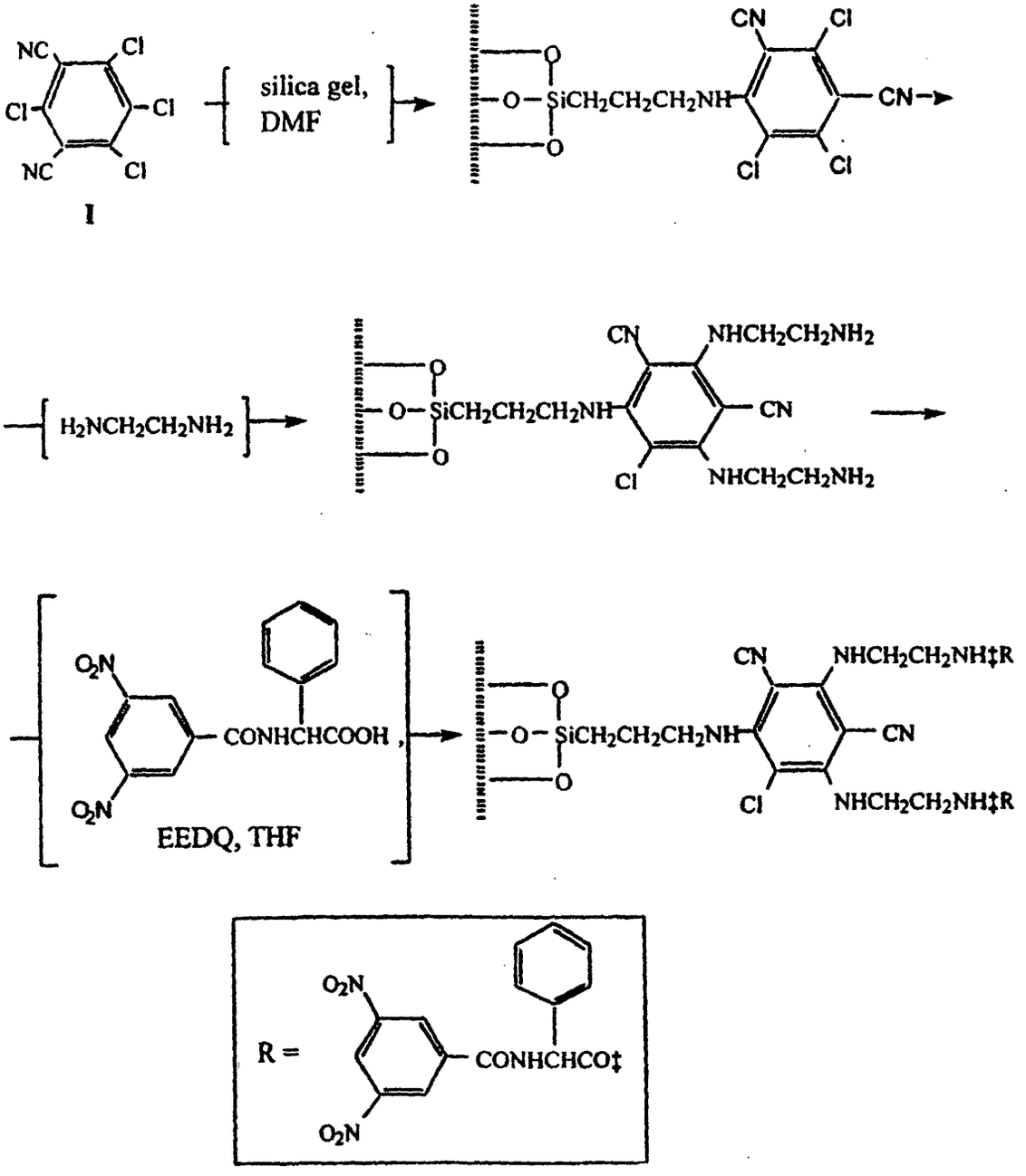

NC
Cl
Cl
Cl
NC
Cl
I
silica gel,
DMF
O
O–SiCH2CH2CH2NH
O
CN
Cl
CN
Cl
Cl
H2NCH2CH2NH2
CN
NHCH2CH2NH2
CN
Cl
NHCH2CH2NH2
O2N
CONHCHCOOH
O2N
EEDQ, THF
NHCH2CH2NH‡R
NHCH2CH2NH‡R
R =
CONHCHCO‡

Figure 5a

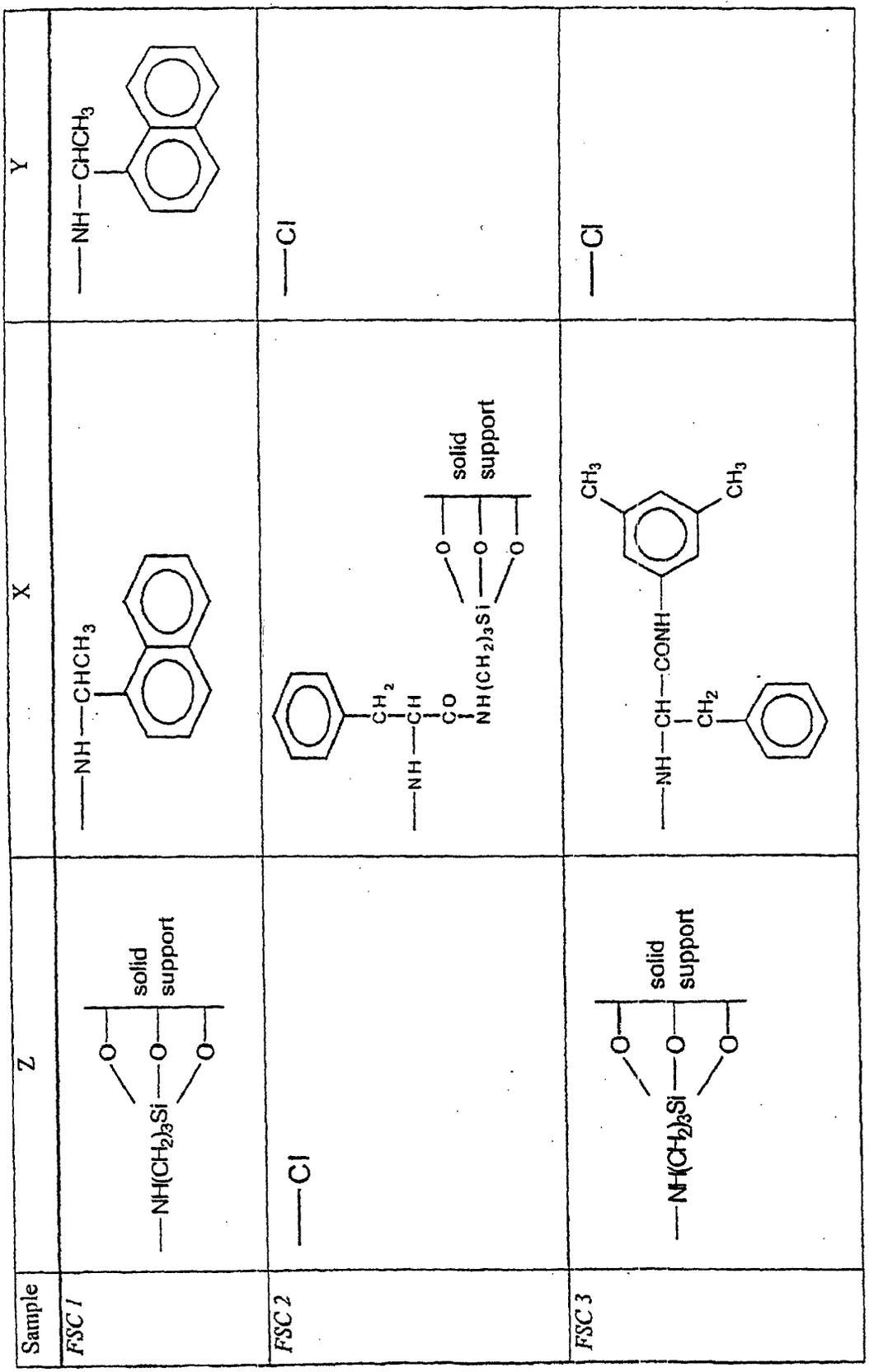

Sample
Z
X
Y
FSC 1
FSC 2
FSC 3
solid support
Cl
CH3
CH2
CH
CO
NH
CONH
O
Si

Figure 5b

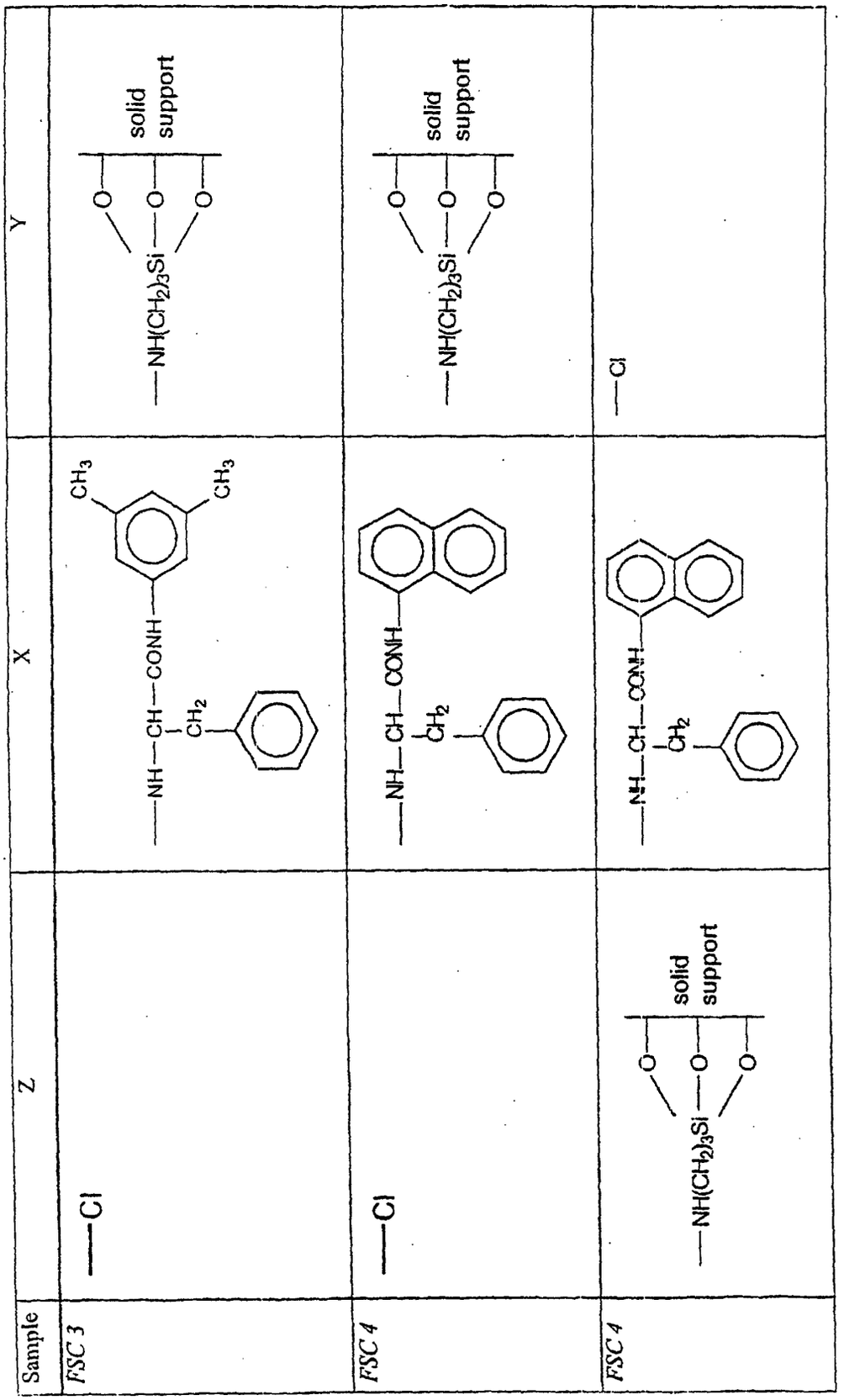

Sample
Z
X
Y
FSC 3
—Cl
—NH—CH(CH2)—CONH—
CH3
CH3
CH2
—NH(CH2)3Si—O—O—O—
solid support
FSC 4
—Cl
—NH—CH(CH2)—CONH—
CH2
—NH(CH2)3Si—O—O—O—
solid support
FSC 4
—NH(CH2)3Si—O—O—O—
solid support
—NH—CH(CH2)—CONH—
CH2
—Cl

Figure 5c

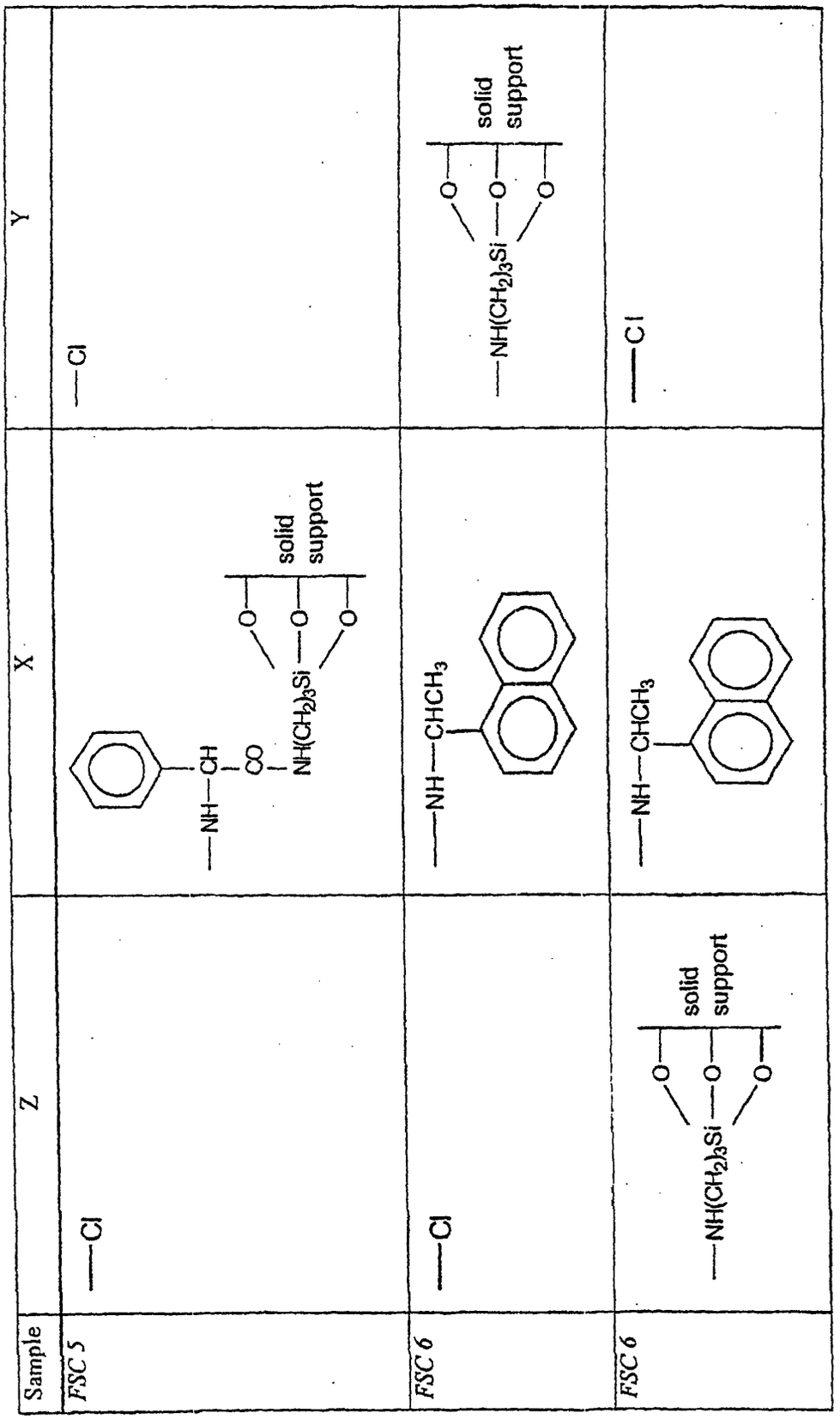

Sample
Z
X
Y
FSC 5
—Cl
—NH—CH(CH3)—O—C(=O)—NH(CH2)3Si(—O—)3 solid support
—Cl
FSC 6
—Cl
—NH—CHCH3
—NH(CH2)3Si(—O—)3 solid support
FSC 6
—NH—CHCH3
—Cl

Figure 5d

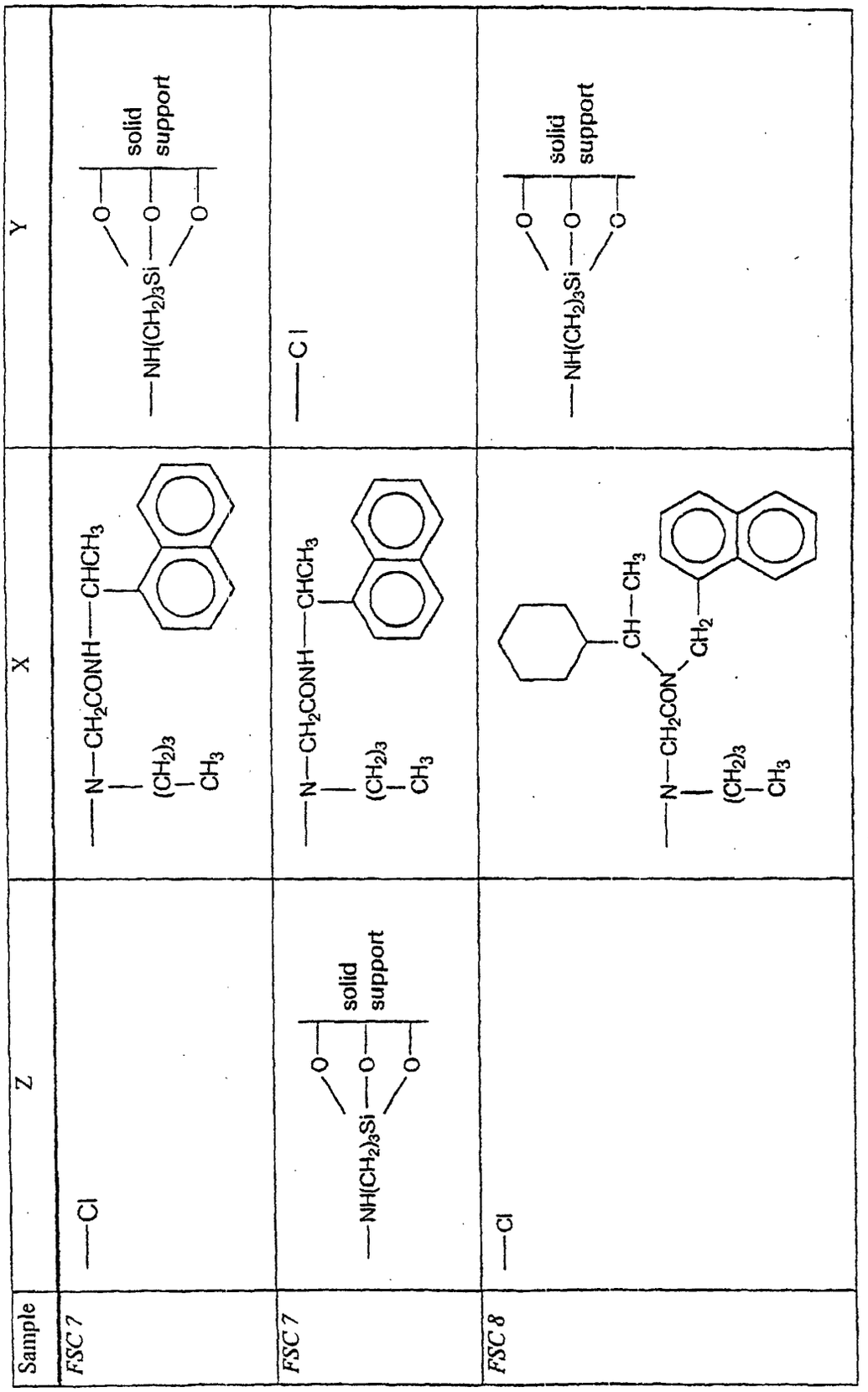

Sample
Z
X
Y
FSC 7
—Cl
—N—CH2CONH—CHCH3
(CH2)3
CH3
—NH(CH2)3Si—O—solid support
FSC 7
—NH(CH2)3Si—O—solid support
—N—CH2CONH—CHCH3
(CH2)3
CH3
—Cl
FSC 8
—Cl
CH—CH3
CH2
—N—CH2CON
(CH2)3
CH3
—NH(CH2)3Si—O—solid support

Figure 5e

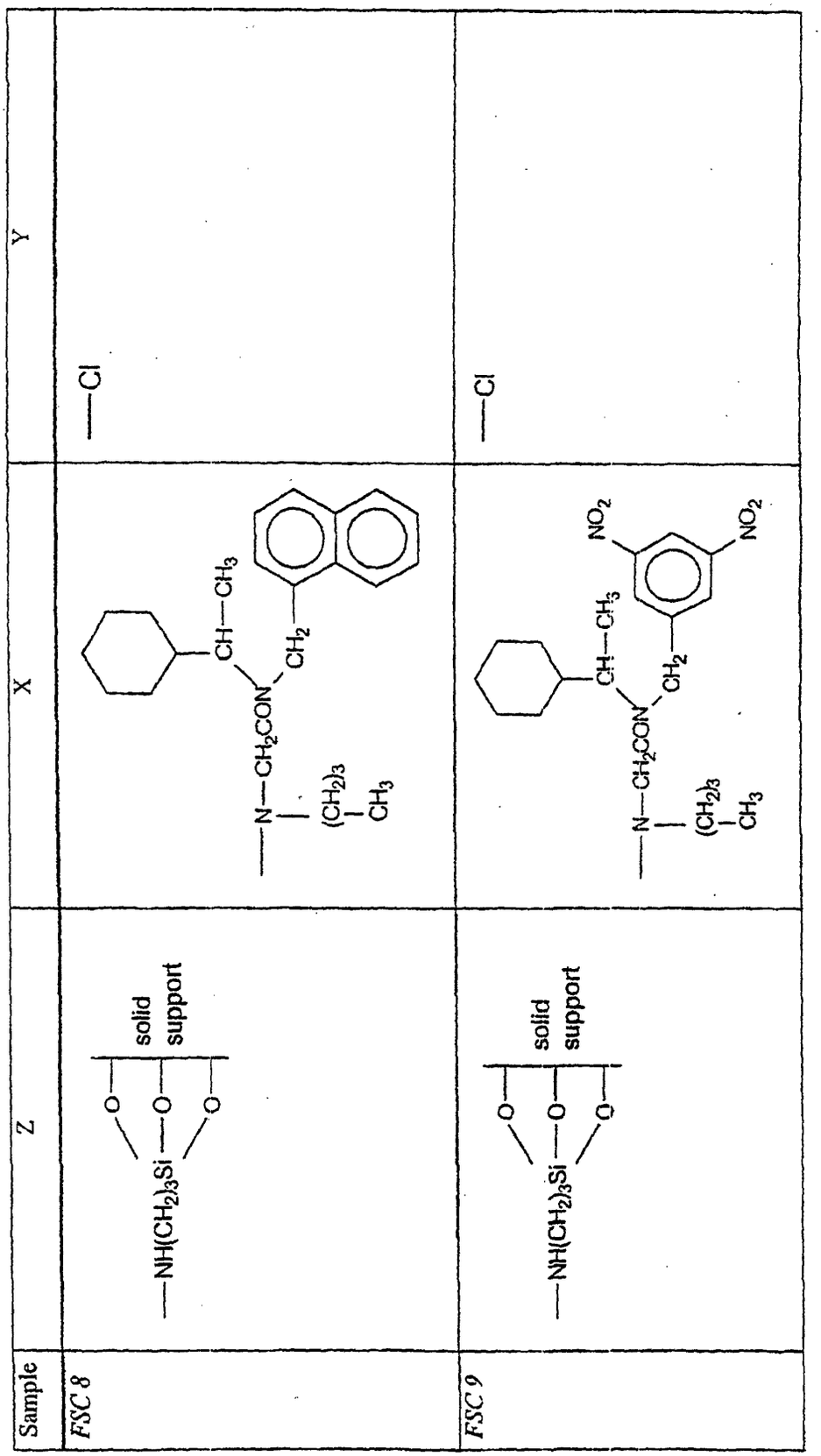

Sample
Z
X
Y
FSC 8
solid support
NH(CH2)3Si
O
O
O
CH
CH3
CH2
N
CH2CON
(CH2)3
CH3
Cl
FSC 9
solid support
NH(CH2)3Si
O
O
O
NO2
NO2
CH
CH3
CH2
N
CH2CON
(CH2)3
CH3
Cl

Figure 5f

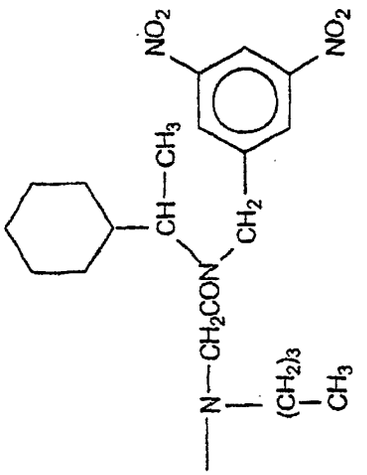
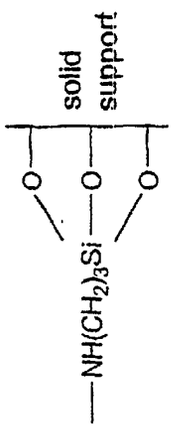
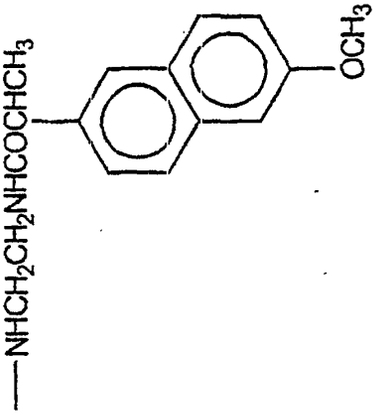
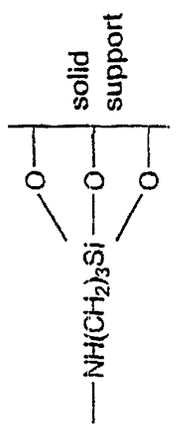
Sample	Z	X	Y
FSC 9	—Cl		
FSC 10	—Cl		

Figure 5g

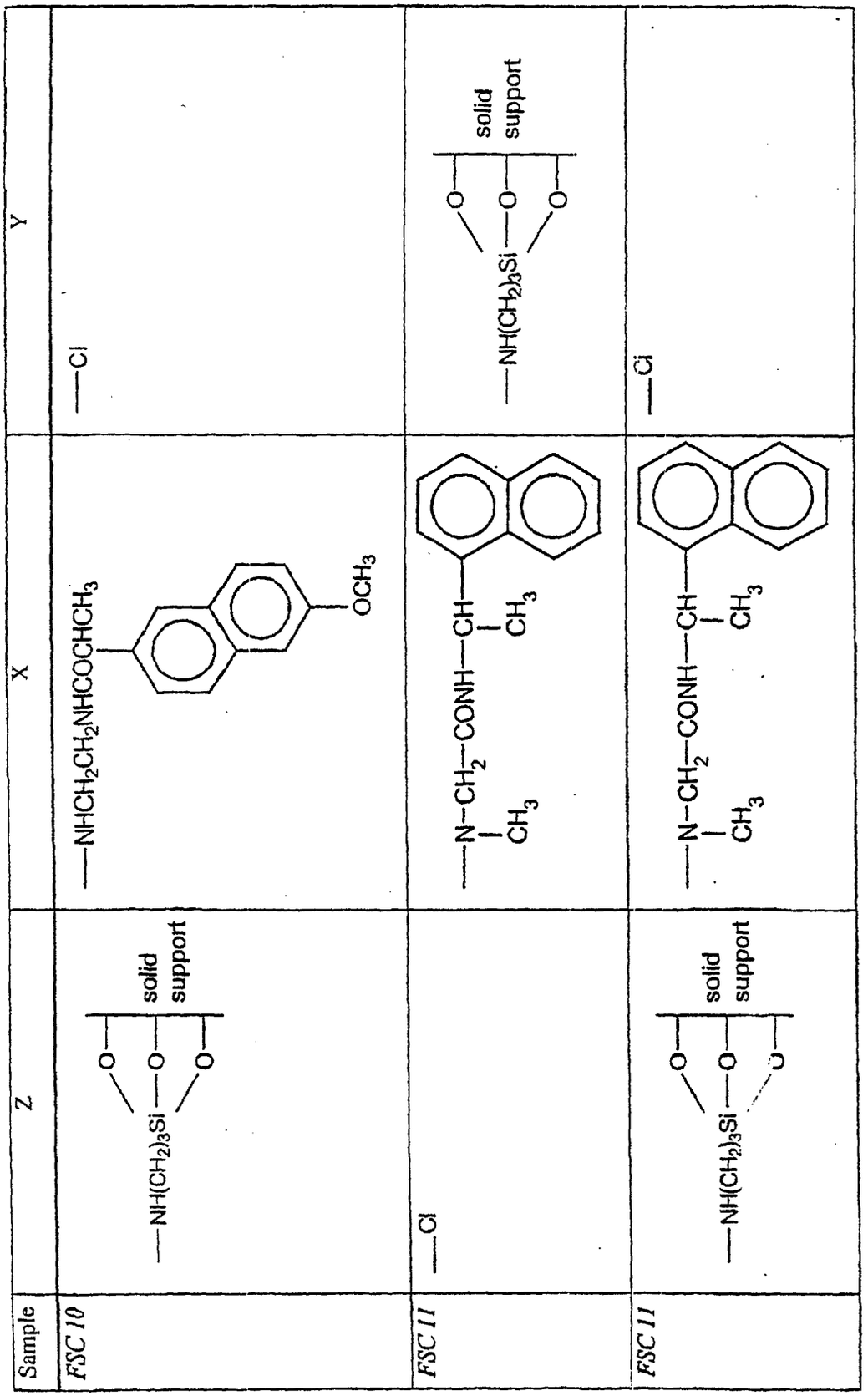

Sample
Z
X
Y
FSC 10
—NH(CH2)3Si
O
O
O
solid support
—NHCH2CH2NHCOCHCH3
OCH3
—Cl
FSC 11
—Cl
N—CH2—CONH—CH
CH3
CH3
—NH(CH2)3Si
solid support
FSC 11
—NH(CH2)3Si
solid support
—Cl

Figure 5h

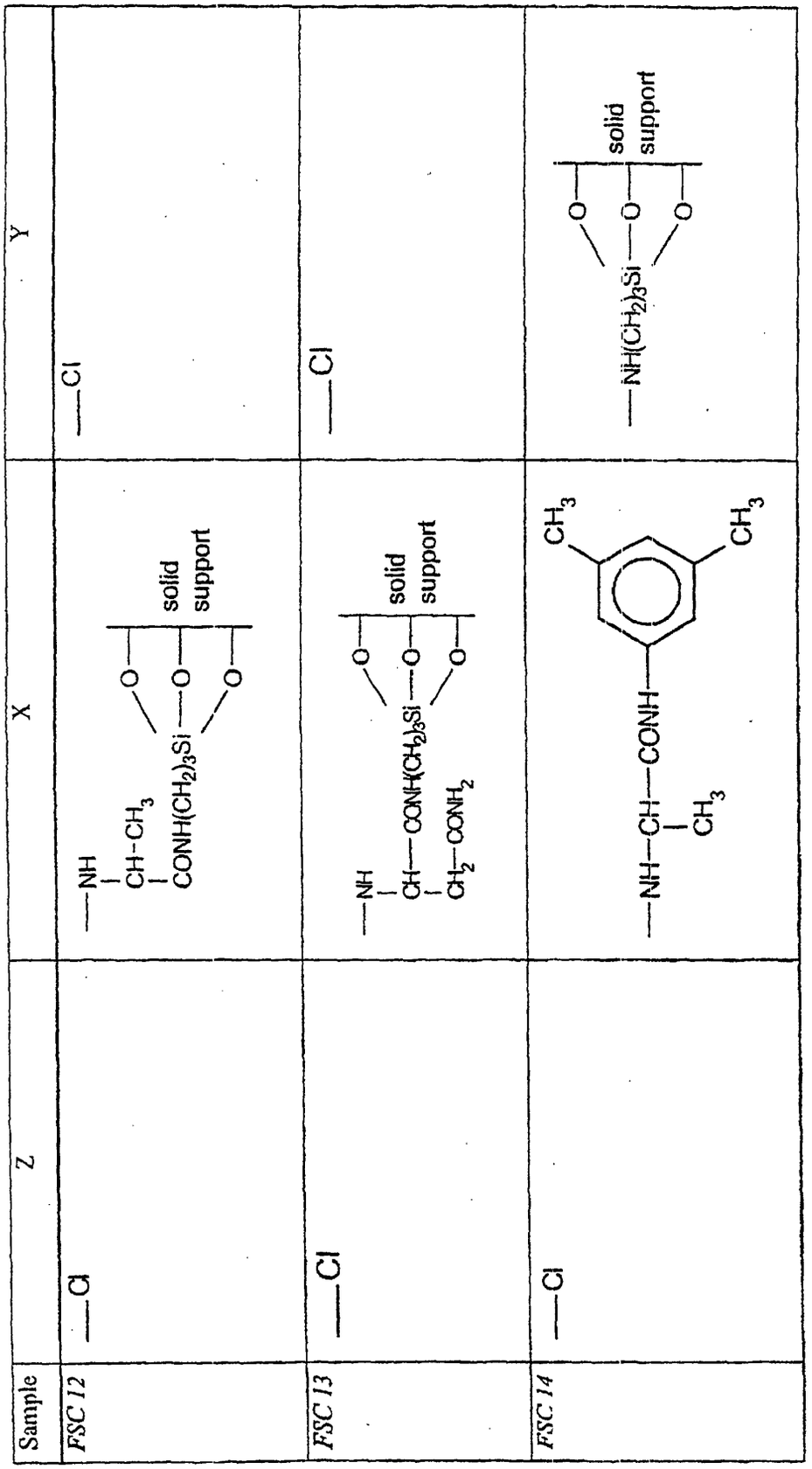

Sample
Z
X
Y
FSC 12
—Cl
—NH
CH-CH3
CONH(CH2)3Si
O
O
O
solid support
—Cl
FSC 13
—Cl
—NH
CH—CONH(CH2)3Si
CH2—CONH2
O
O
O
solid support
—Cl
FSC 14
—Cl
CH3
CH3
—NH—CH—CONH—
CH3
—NH(CH2)3Si
O
O
O
solid support

Figure 5i

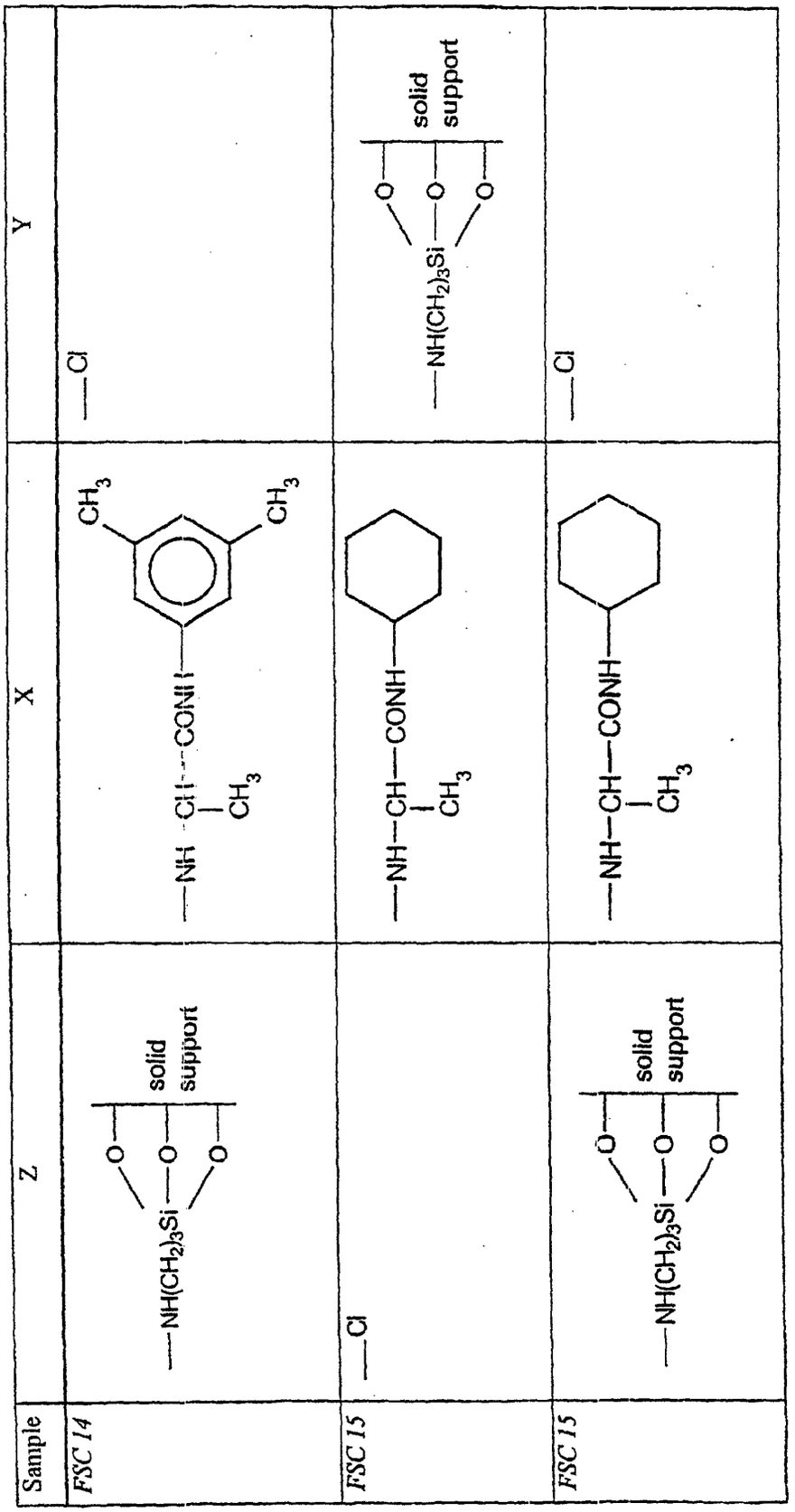

Sample
Z
X
Y
FSC 14
—Cl
FSC 15
—Cl
FSC 15
—Cl
solid support
—NH(CH2)3Si
—NH—CH—CONH—
CH3

Figure 5j

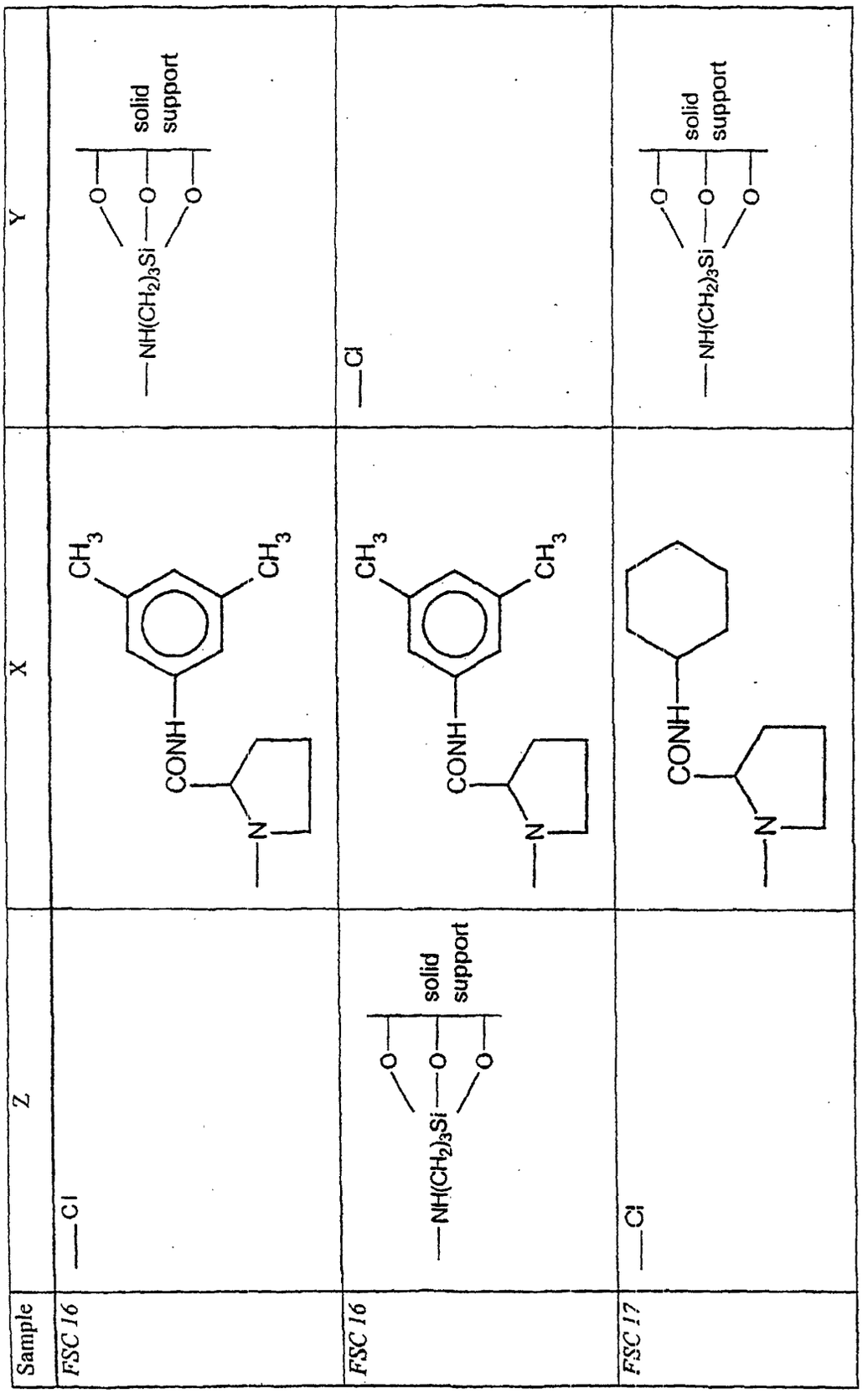

Sample
Z
X
Y
FSC 16
—Cl
CONH
N
CH3
CH3
—NH(CH2)3Si
O
O
O
solid support
FSC 16
—NH(CH2)3Si
O
O
O
solid support
CONH
N
CH3
CH3
—Cl
FSC 17
—Cl
CONH
N
—NH(CH2)3Si
O
O
O
solid support

Figure 5k

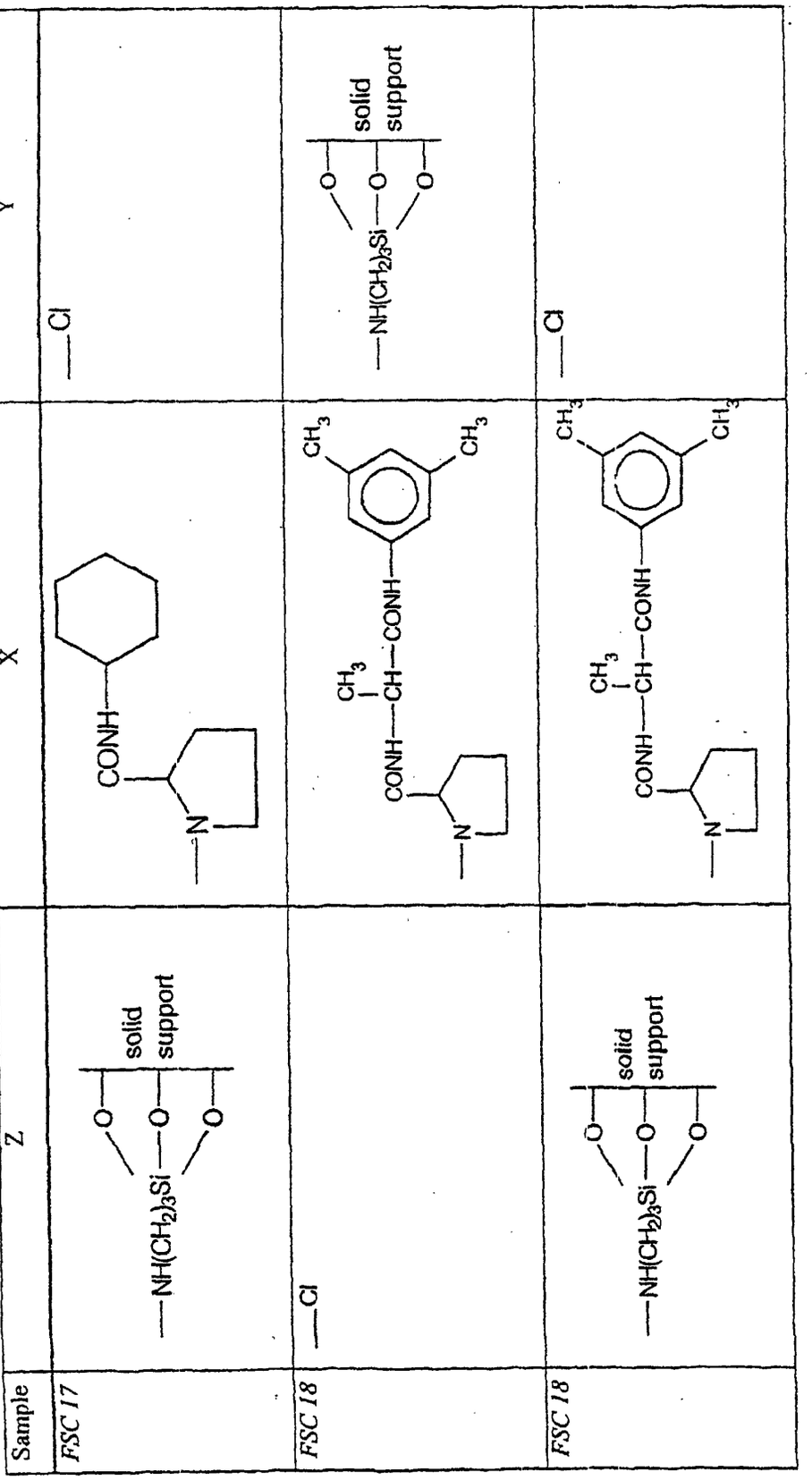

Sample
Z
X
Y
FSC 17
—Cl
solid support
—NH(CH2)3Si
CONH
N
FSC 18
—Cl
CH3
CONH
FSC 18
—Cl
solid support
—NH(CH2)3Si
CH3
CONH
N

Figure 5l

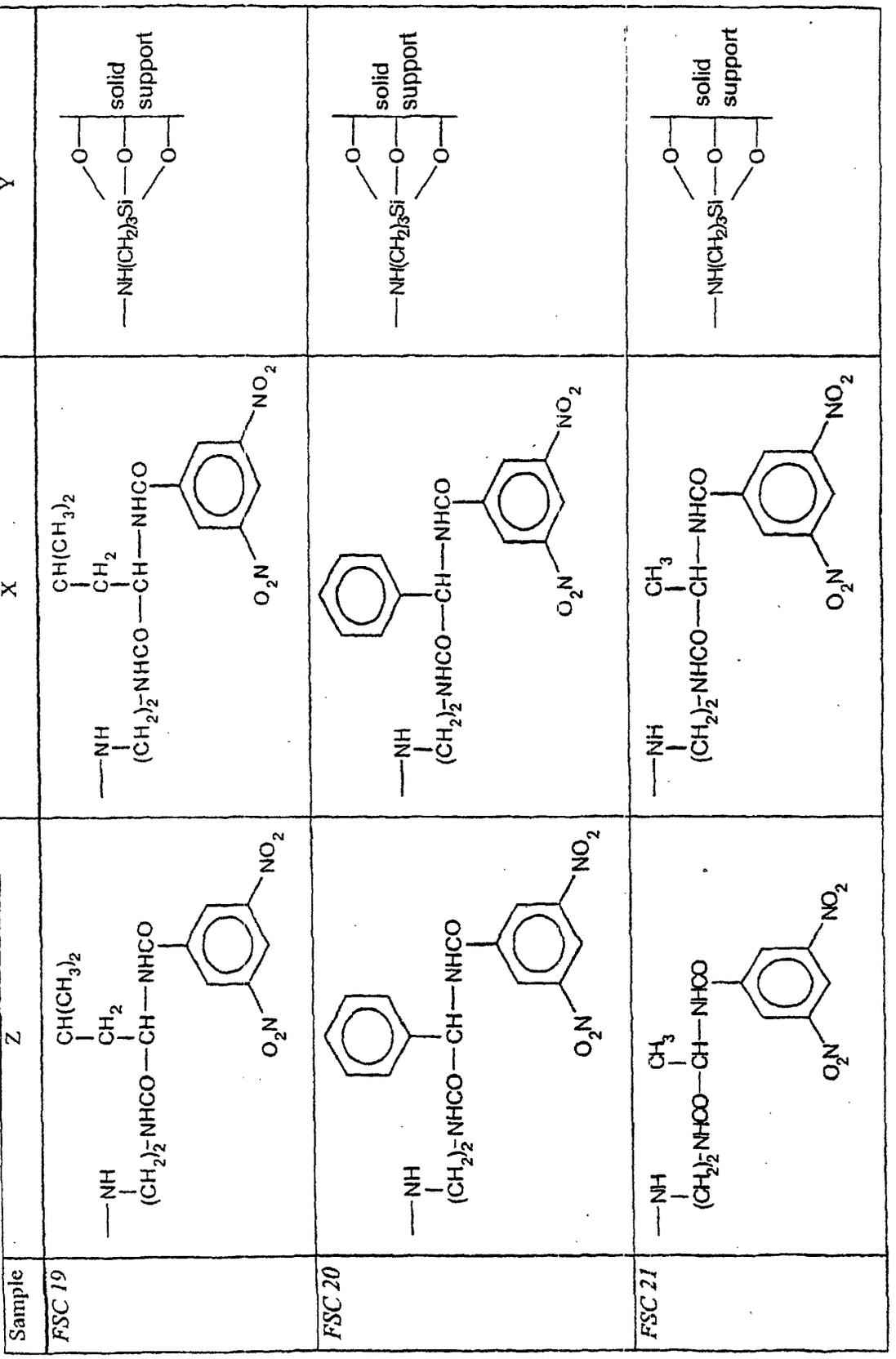

Sample
Z
X
Y
FSC 19
FSC 20
FSC 21
solid support
NO2
O2N
NHCO
NH
CH2
CH3
CH(CH3)2

Figure 5m

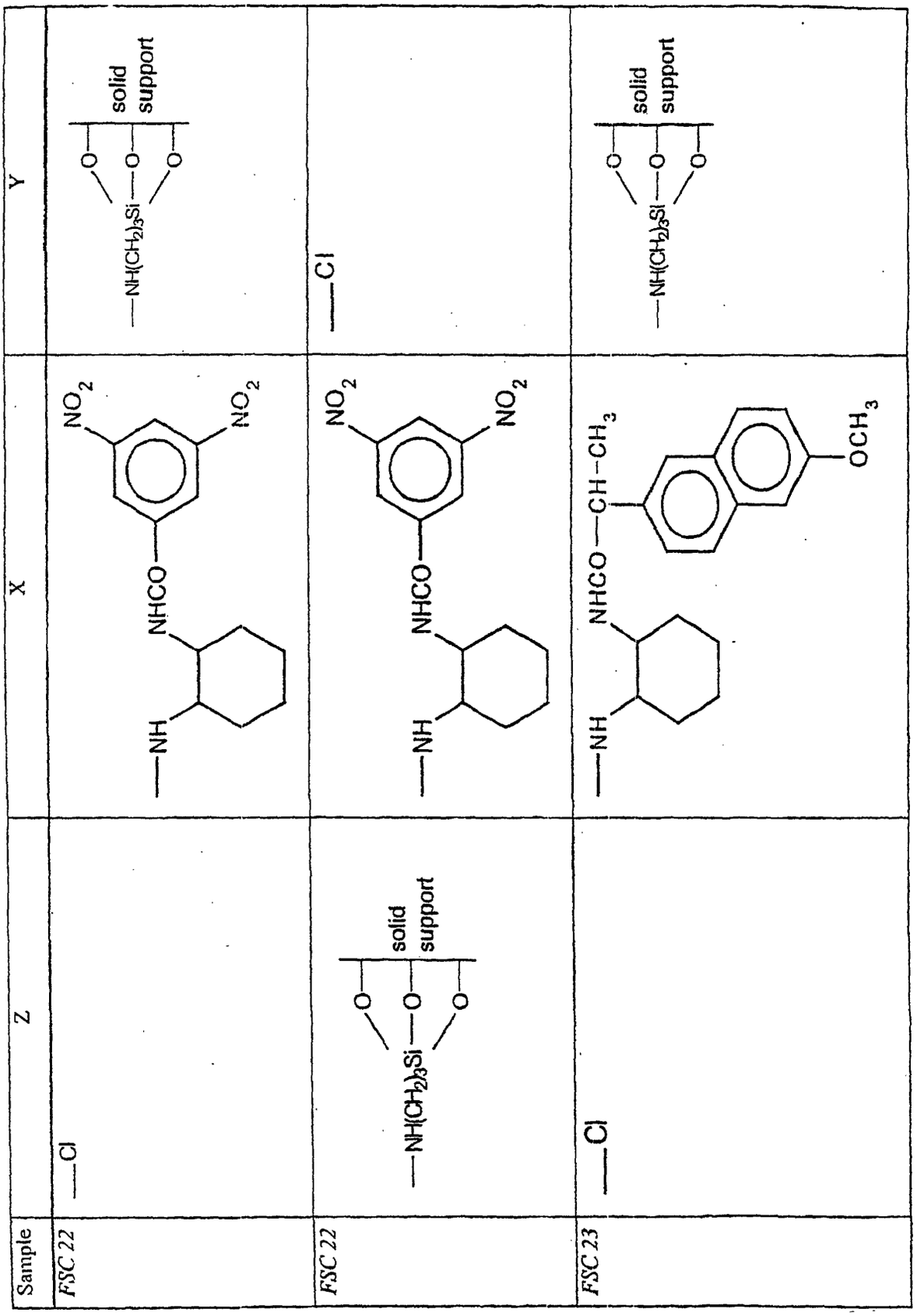

Sample
Z
X
Y
FSC 22
—Cl
NO2
NO2
NHCO
NH
—NH(CH2)3Si
O
O
O
solid support
FSC 22
—NH(CH2)3Si
O
O
O
solid support
NO2
NO2
NHCO
NH
—Cl
FSC 23
—Cl
NHCO—CH—CH3
NH
OCH3
—NH(CH2)3Si
O
O
O
solid support

Figure 5n

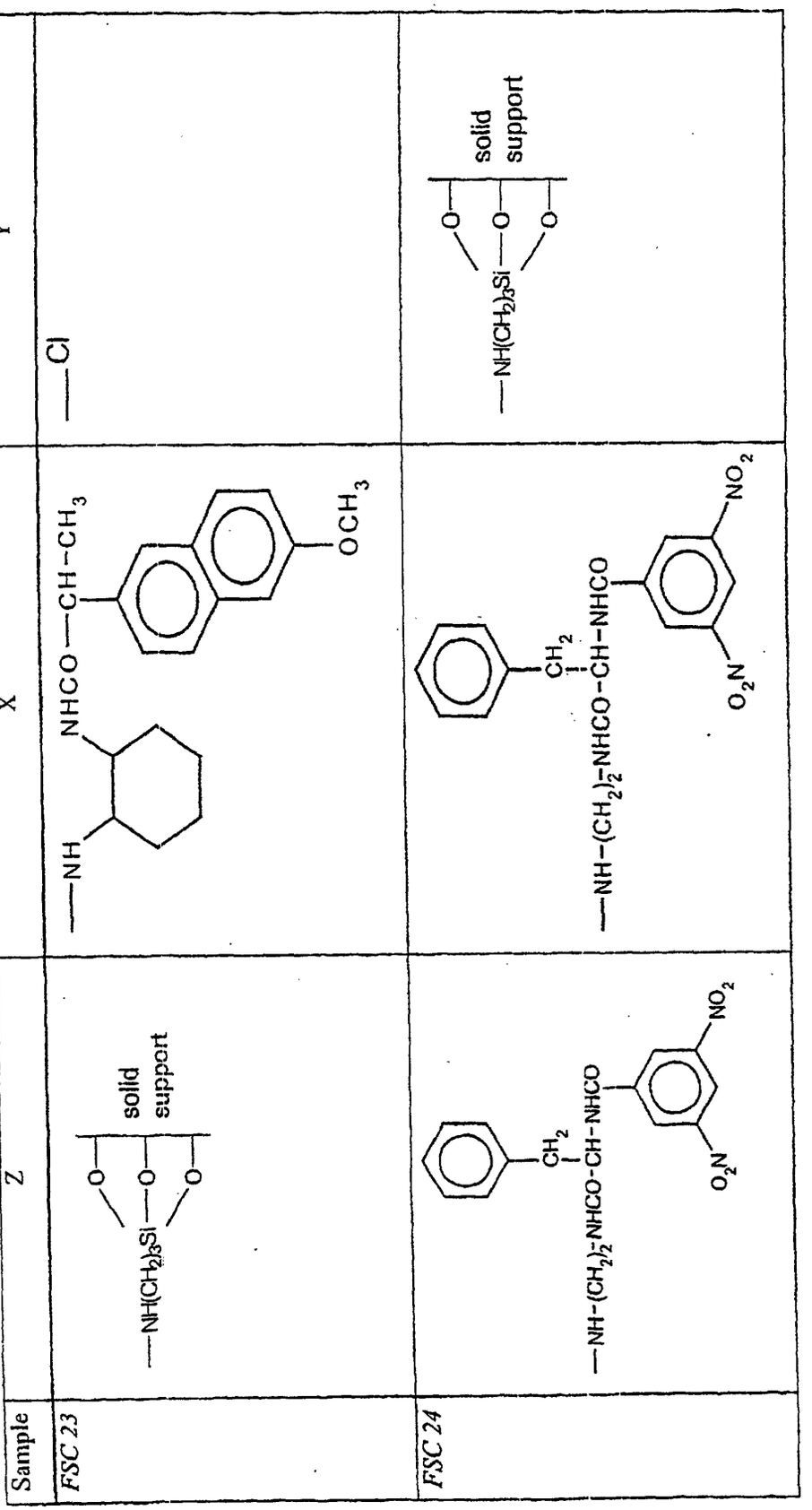

Sample
Z
X
Y
FSC 23
solid support
NH(CH2)3Si
NH
NHCO
CH-CH3
OCH3
Cl
FSC 24
solid support
NH(CH2)3Si
CH2
NH-(CH2)2-NHCO-CH-NHCO
NO2
O2N

Figure 5o

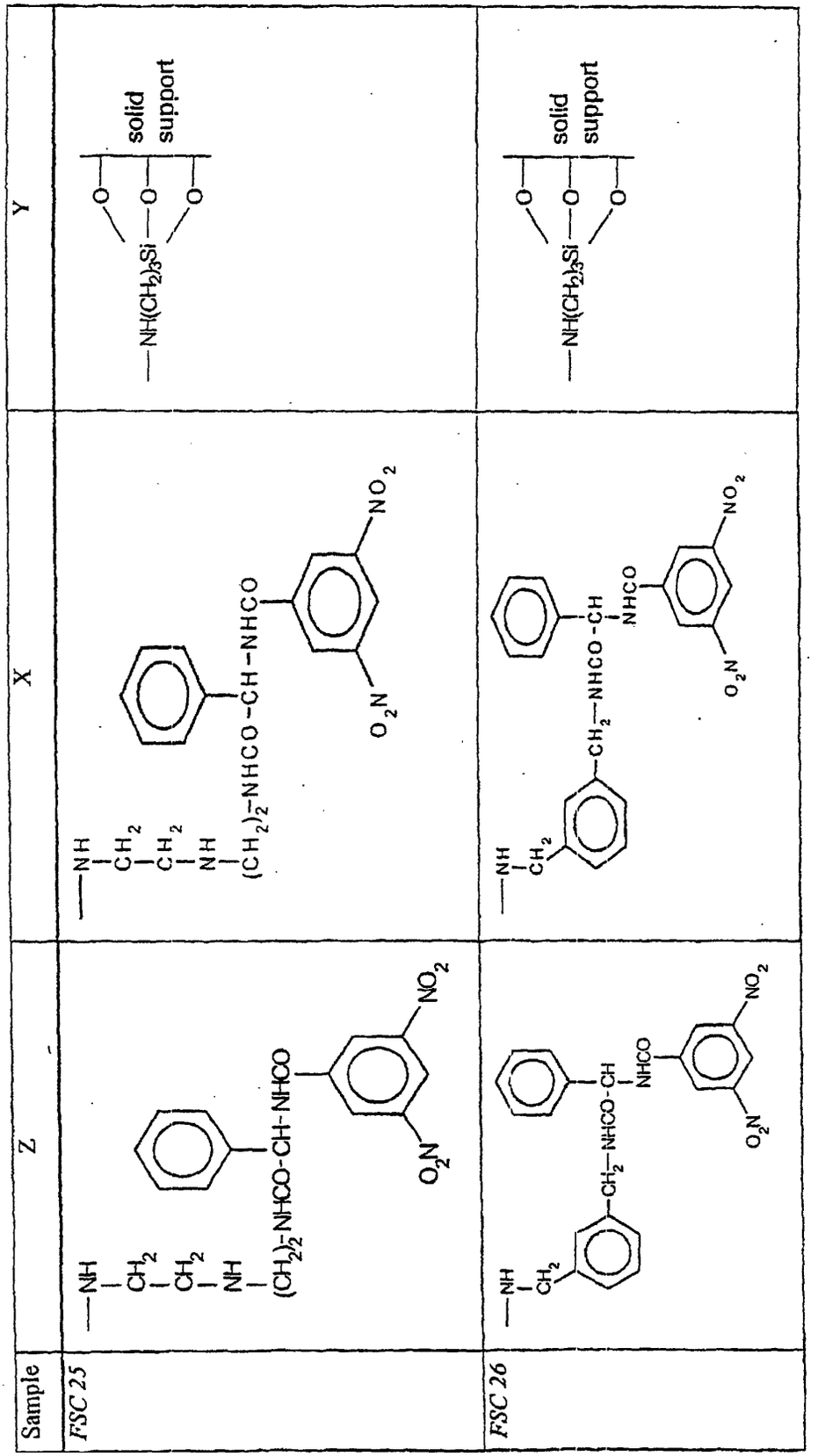
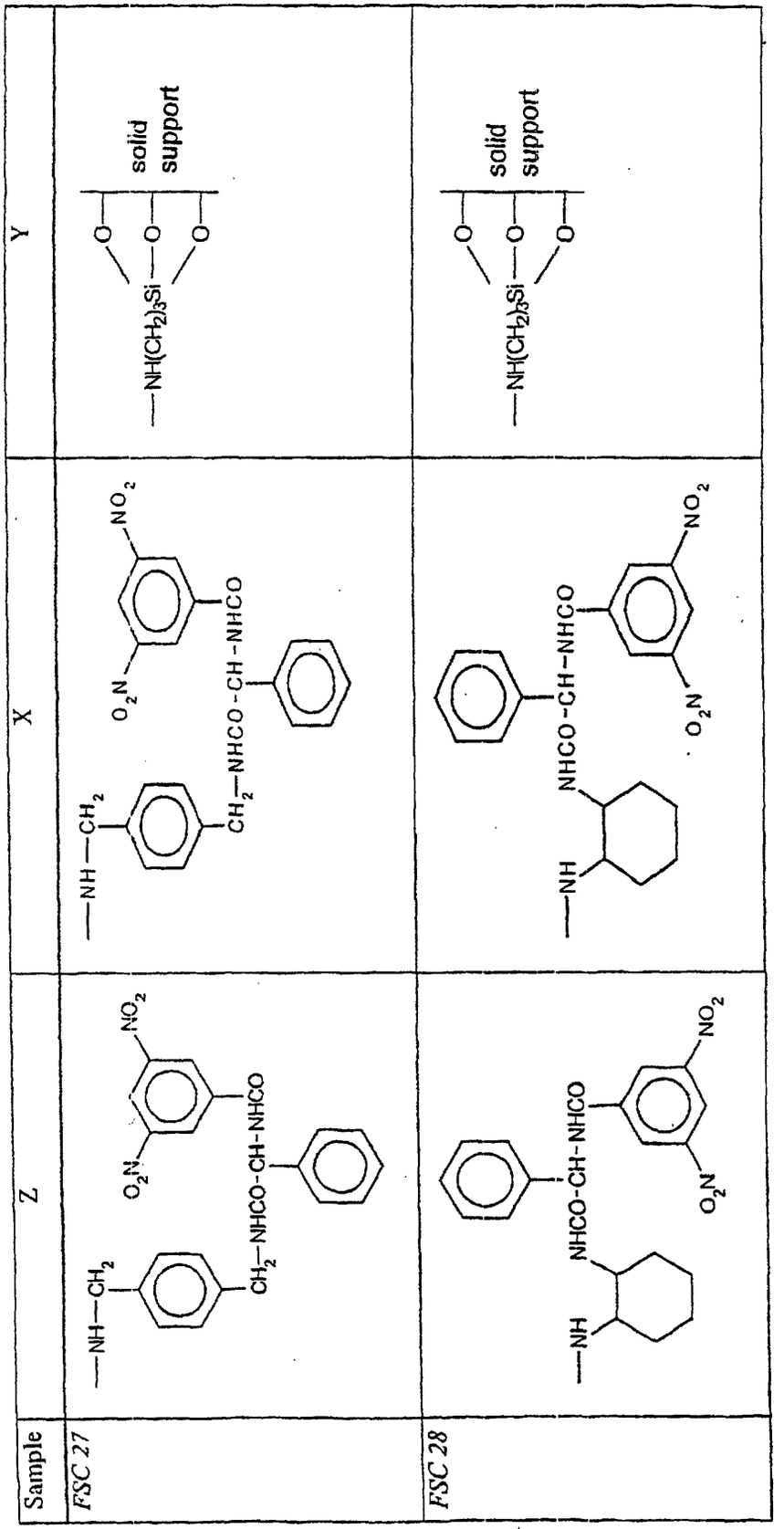
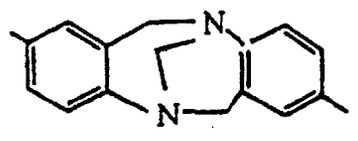
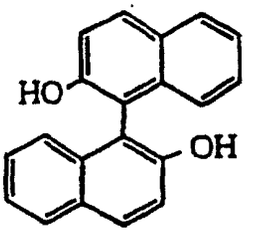


Figure 5p


Sample
Z
X
Y
FSC 27
FSC 28
solid support
NH(CH2)3Si
O2N
NO2
NHCO-CH-NHCO
CH2
NH



TR 6



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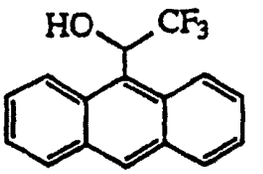

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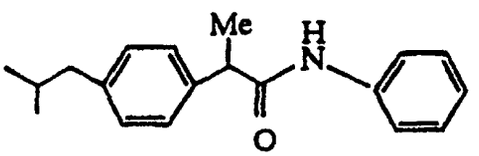
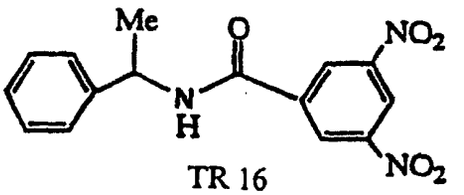
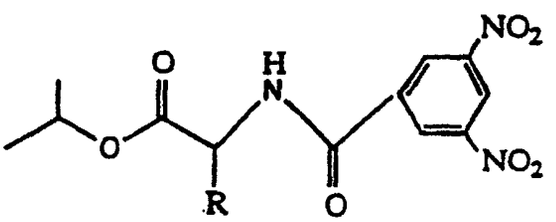


TR 15



TR 16



TR 17 R=Ala
TR 18 R=Val
TR 19 R=Leu
TR 21 R=Phgly
TR 22 R=Phe
TR 23 R=Met

Figure 6